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# The Challenge of the "Well Child"

ALVIS JOE SCULL, M.D., San Francisco

*• Upon general practitioners and pediatricians falls the responsibility of recognizing and treating most emotional problems in young children. This may be best carried out by the anticipation of expected problems, and the advance guidance or counseling of parents. That such problems are of high incidence was indicated in experience at a pediatric clinic where approximately 40 per cent of 7,000 children observed had psychosomatic symptoms.*

*In order to utilize effectively the limited time available in office practice for Well Child care, a physician must have at hand certain basic information on personality development. Many of the normal behavior patterns in children which frequently are misinterpreted as "behavior problems" by parents are presented herein in chart form, divided into critical age periods, to help physicians quickly recognize what is normal and what abnormal in various periods of maximal crisis. Most of the problems of conflict within a child and of conflict between parents and child, it is felt, could be and should be handled at the pediatric level. Some seriously disturbed children need to be referred for psychiatric care. When this is necessary, skillful preparation of the parent and the child by the family physician for referral is most important to successful psychotherapy.*

IN RECENT YEARS physicians have become aware of the need for preparation in the management of everyday problems of emotional growth and personality development. The increasing complexity of family life, emotionally and economically, places tremendous responsibility on the family physician, be he pediatrician or general practitioner, to recognize such problems and to advise as to appropriate and effective means of management.

It has been established by survey[1] that Well Child care represents an important demand placed upon the practitioners of medicine. Pediatric specialists are obligated to spend approximately one-half to two-thirds of their professional time giving Well Child care. General practitioners spend approximately 30 per cent of their time giving pediatric care, although for various reasons, only 5 to 10 per cent in Well Child supervision. Furthermore, the responsibility for the medical care of the children in a community resides, for the most part, with general practitioners, who are first to observe approximately 75 per cent of children for whom medical advice on a private basis is sought.

A recent postgraduate conference of general practitioners and pediatricians held at Stanford University School of Medicine emphasized this fact as an effort was made to evaluate and understand better the actual problems of physicians in practice. The interests were two-fold:

1. What are the behavior problems for which parents most frequently seek help?

2. How many and which of these problems can

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and should be effectively handled by the family physician at the pediatric level?

After two weeks of intimate association between the postgraduate group and a group of discussion leaders chosen from the fields of pediatrics and child psychiatry, some strong impressions were formed as to how educators might better prepare physicians in training for their roles as counselors of parents.

The problems of the organically well child about which these physicians felt uncomfortable or inadequately prepared to give advice were scrutinized and the Pediatric Department of Stanford University set up a comprehensive Well Child program in the Out-Patient Children's Clinic which is designed to meet the specific needs for orienting its medical students and residents to the demands that will be made upon them when they emerge into practice. The thought was expressed by many of the practicing physicians that more time devoted to the explanation of *how* a personality develops and what pitfalls can be expected at various age levels would be helpful. If each age level could be exposed and analyzed thoroughly, they felt it would help them understand *how a child thinks and feels* at a given age and thus *why he develops* disturbing behavior. It was felt that if one can better understand the child *thought patterns* and how they develop, then one can better understand the child and thus more effectively help him and his parents. Men so trained can be better prepared to comfortably and effectively advise mothers in the everyday problems of raising normal, healthy babies and to manage the psychosomatic aspects of their illnesses. Undergraduate medical education in the past has not adequately stressed this role which students will be called upon to play as practitioners of medicine.

It seemed, therefore, that a review of observations in the Stanford Children's Clinic might demonstrate the problems of dealing with the Well Child and serve as a guide for physicians in private practice. In a survey of the cases of 7,000 children observed in the Children's Clinic, it was noted that 40 per cent of the children who were observed as "new" patients had emotional problems to a degree that interfered with or prevented institution of somatic therapeutic measures that otherwise might be successful.

The cases of 755 children registered in the Out-Patient Clinic as "new" patients in a period of six months were reviewed. The children were observed and interviewed by students under the supervision of staff consultants. Patients were classified into four groups:

1. Well children with no complaint who came into the clinic for routine check-up and who, after a complete history and physical examination were done, seemed healthy, happy and well adjusted. (Obviously the percentage in this category would be expected to be much lower than in a comparable group in private practice.)

2. Children whose chief complaint proved to be entirely on an organic basis with no emotional conflicts apparent to the examiner or his consultants.

3. Children who came with a chief complaint referable to organic disease, but in whom there were psychosomatic overtones or emotional factors of sufficient magnitude to interfere with or prevent institution of definitive therapeutic measures.

4. Children whose chief complaint was of emotional or psychic origin without any organic factors of significance in either etiology or management.

The numbers of cases of each classification were as follows:

| | No. of cases | | Per cent | |
|---|---|---|---|---|
| 1. Well without complaints | 93 | | 12.3 | |
| 2. Organic problems | 346 | | 45.8 | |
| 3. Psychosomatic problems | 277 | 316 | 36.7 | 42 |
| 4. Emotional or behavior problems | 39 | | 5.2 | |

Of the 316 children who had problems relative to emotional inadequacies or who were psychosomatically disturbed, 39 who were considered to be too seriously disturbed for treatment on a pediatric level in the Children's Clinic were referred to the Child Guidance Clinic for consultation and psychotherapy. However, as 28 of the 39 were subsequently given treatment by two Pediatric Fellows in the Child Guidance Clinic, there were, in all, 288 children who were given some degree of psychological attention by the pediatric staff.

In light of the rather high incidence of emotional problems, obviously the matter is one for serious consideration by pediatricians and family physicians.

What are the reasons for hesitancy on the part of pediatricians or general practitioners to give counsel to parents when deviations from the normal behavior patterns begin to appear? (1) The feeling that there is not time available to them is a prominent factor in this attitude. (2) Lack of confidence in their own ability of judgment as to what can be constituted as "normal" undoubtedly plays a role. (3) Because of the tension and pressure under which physicians work in private practice, it may be that many cases of early deviations from normal developmental patterns are unrecognized in their incipient stages. Hence, only more seriously disturbed family situations are noticed by the physician, and these are understandably more complex than should be undertaken by him for treatment.

Against these factors, however, must be considered the many reasons why the general practitioner or the pediatrician is in a strategic and unique posi-

CHART 1

**Normal Behavior Patterns of Children Which Appear as or Precipitate Problems for Parents**

| DEVELOPMENTAL AREAS | Age 1-3 Months | 3-6 Months | 6-9 Months | 9-12 Months |
|---|---|---|---|---|
| MOTOR | | | Sitting, creeps. | Crawls, pulls up, walks alone. |
| LANGUAGE | | | | |
| SOCIAL | Smiles with stimulation. | Interested in attention from others; spontaneous smiles; recognizes desertion—cries if left. *Thumbsucking.* | *Shy—recognizes and fears strangers;* responds to familiar people; responds to play. | Anger— *Breath holding first appears.* |
| FEEDING | Nursing— ? breast or bottle. Spitting up, colic. | Starting solid foods; may fight spoon. (Go easy.) | Holds bottle alone; usually big appetite. Often refuses solids, however (negativism). | Messy eater, finger-feeds self; long retention of food; refuses bottle often. *11-month abrupt decrease in appetite.* |
| SLEEP | Irregular patterns. | Teething. | Rhythm movements; good to rock to sleep. | Sleep resistant (10 mo.). |
| TOILET HABITS | | Bowel irregularities. | Frequent efforts at toilet training. | |
| SEXUAL | | | | Genital play if undiapered. (Self-discovery.) |

tion to render effective service to any given family. (1) The family has great confidence in him as physician and advisor. (2) The family physician already knows a great deal about the total family situation and personal idiosyncrasies which could be weeks or months coming to light in a psychiatric setting. (3) There is, unfortunately, still a strong feeling among the lay public that a stigma is attached to placing oneself in the hands of a psychiatrist for advice or consultation. (4) Often, frequent short interviews with reassurance from the family physician can so fortify or reinforce parents that they are able to work successfully through rather difficult and trying situations. (5) Families will consult the family physician about little problems, whereas they will not go to a psychiatrist unless the child is seriously disturbed.

In helping parents to understand, avoid, or properly handle those periods of maximal crisis that normally appear during the course of the growth and personality development of their child, it is imperative that such periods be recognized and well understood by the counseling physician.

To understand more effectively the normal patterns of personality formation, it is well to recognize that every child faces a series of specific tasks or goals, each of which must be mastered or achieved before he is able to proceed to the next step in his development as a secure, happy and well adjusted person.[5, 8] Although many of the patterns are normal they entail behavior which will, in parents or other adults who do not appreciate that fact, precipitate conflicts in interpersonal relationships, which in turn result in or appear as behavior problems. It is at the time of such crises in behavior that informed physicians can often untangle the misunderstanding and relieve the tension in the home, in the child and the parent, thus eliminating problems which, if ignored or mishandled through efforts at discipline or punishment, will result in more serious personality problems and "problem children."

Briefly, the developmental tasks are as follows:

*Developmental Tasks*[8] *of Infancy* (Charts 1 and 2)

During the period of infancy, there occurs a very definite pattern of differentiation of the emotions in the child as well as a definite pattern of motor control. At around three months the infant's smile at his mother acquires social significance. By six months, the infant is quite clearly capable of experiencing also fear, anger, and disgust.[2, 3, 5] At about six months and again at around twelve months, he may show a fear of strangers,[2, 4, 6] or at least recognize and distinguish between familiar and strange persons.

By the end of the first year the child may show his affection for his parents and during the next five or six months may demonstrate definite evidence of affection or jealousy toward other children.[5]

Around two years, the child begins to feel extremely dependent upon his mother and a prolonged separation from her at this time creates a great deal of anxiety within him which may be highly traumatic.[2, 3, 4] During the second year, owing to frequent interferences with his physical activities and because of his own impatience with his lack of

CHART 2

**Normal Behavior Patterns of Children Which Appear as or Precipitate Problems for Parents**

| DEVELOPMENTAL AREAS | Age 12-15 Months | 15-18 Months | 18-21 Months | 21-24 Months |
|---|---|---|---|---|
| MOTOR | | | | Runs well; goes up and down stairs alone. |
| LANGUAGE | | | | Uses pronouns: I, you, me. Stuttering common, not significant. |
| SOCIAL | Jealousy appears.<br>Hyperactive—into everything.<br>"Bites" frequently. | Sensitive—avoid shaming and punishment as yet; parents prone to expect too much conforming to adult standards. | Tendency to run around nude—shame too often used. Negativism; learning to control people; *temper tantrums appear.*<br>Frequent waking, demands. | *Negativism increased;* accept without retaliation; temper tantrums persist. Shy of strangers, but adjusts quickly if not pressed.<br>*Strong fear of desertion.* Good to sing or rock to sleep. Sitter troubles—avoid trips away unless baby along. |
| FEEDING | Grabs at dishes, cups; messy eater. | Wants to feed self, spills; must eat when hungry, can't wait at all. Changes food likes, dislikes.<br>*Peak of thumbsucking (as tension outlets?).* | Good appetites; if easily distracted—feed before others.<br>Strong food preferences. | Finicky about foods: color, taste, or consistency. |
| SLEEP | Wakeful at nights—1-2 hours often. | | Frequent waking at nights, not fear.<br>Numerous demands.<br>Pleasure of using words. | |
| TOILET HABITS | If regular—try training; starting sphincter control; fear of toilet noises.<br>Plays with feces if undiapered or loosens diapers.<br>Urge use of potty chair. | May resist if just starting toilet training. | Smearing of stools, especially after naps. Girls beginning to stay dry—not boys.<br>Boys often demand to be fully undressed before will try bowel movement. | Strong fear of bed-wetting; never punish—reassure.<br>Usually toilet trained by by now. |
| SEXUAL | | | | |
| SCHOOL | | | | Only if unavoidable; need good introduction with mother along. Short attendance periods—avoid overstimulation; don't expect participating play. |

ability, angry outbursts are likely to be frequent. Throughout infancy emotional reactions occur, characteristically brief and transitory, although they may be intense.

The parents should be prepared for temper tantrums, which occur most frequently at this age. There is also an exaggerated fear of separation from the parents. This is normal, for the child is very dependent upon them. Parents should avoid trips of separation that are optional. Any unknown is frightening, too. Careful preparation of the child for any expected family addition is of great importance at this age to minimize jealousy. The first step in the emotional development of the infant is to acquire a sense of security and trust which comes from the successful establishment of complete dependence upon his parents and their acceptance of him. The child who can trust his parents is not afraid to grow up.[4] The child still has fear of strangers at this age, but enjoys social groups of the family, a demonstration of his power of discrimination. This a physician may point out as a compliment to the family; it is the child's recognition of his dependency upon the parents.

The next step in the emotional growth of the infant is to become aware of himself and to develop a concept and feeling about himself as an individual who is distinct from his environment.[5, 8] With experience, by trial and many errors he gradually begins to adjust to the world around him, acquiring more and more control over his own movements and over his environment as his physical abilities develop. He also begins to adjust to his social world so that before the end of his first year he is beginning to

respond to the expectations and demands of others. It is during his second year that he begins to acquire feelings of what (in his behavior) will be tolerated and what is appropriate. This awareness of right and wrong is the beginning of the development of the child's conscience.[5] Parental disapproval or punishment engender a feeling of guilt and shame, while parental support and encouragement lay the foundation for self-confidence and independence.

Most of the social demands made upon an infant during his first year revolve around eating. Even at this early age there may develop conflicts about food —conflicts about, for instance, what or when a child should eat—that may result in anxiety and resentment on the part of both the mother and the child.

Self-feeding by spoon may be allowed, but the mother should be advised not to become annoyed or too greatly concerned about the splashing and playing with food. An insecure child may over-eat in an effort to please his mother or reassure himself that he is loved, while a child in conflict with his mother succeeds in punishing her by his refusal to eat. Because conflicts involving eating serve no useful purpose and often provide the groundwork for emotional disturbances in later life, a physician is carrying out a most important function when he helps parents to guide a child to a more mature and satisfying method of eating with a minimum of friction.

Probably the next source of harmful conflict with an infant is in connection with toilet training or bowel control—especially since toilet training is usually started at about the time when an infant is just becoming aggressive and can experiment with motor control and is beginning to exercise his need to become physically independent of his parents. To undertake bowel training before the child has acquired cortical control over the sphincters (which as a rule occurs in the latter part of the second year[5]) only makes him feel uncomfortable and too often results in a feeling of frustration in the parents.

A physician giving counsel regarding toilet training cannot rely upon the mother's ingenuity but must give logical directions and explanations as to when and why this procedure is advantageous. It is most natural for toilet training to be accomplished at the imitative ages of 18 to 20 months, but blaming and shaming must be avoided.

If too much emphasis is placed on cleanliness, a child may continue to be preoccupied with thoughts about sphincter control long after he should have gone on to other problems of growing up. If a child learns to associate toilet training and elimination functions with disgusting or unpleasant emotions, he may transfer these feelings to his sexual activities. This could eventually handicap him in making a satisfactory sexual adjustment in adult life.

The end of the second year is a critical time for parents. It is only natural to begin to expect "too much" of a child at this age, and to become concerned and confused as to discipline, obedience and authority. It is most important to recognize that the child needs (1) the joy of achievement and (2) the approval of his successes to enable him to go on to the developmental tasks of his next stage.[5, 8] Parents need acceptance, understanding and support by their physicians, too.

During his second year a child often discovers that he has a mind of his own; he wants to think for himself, to make his own decisions, and he begins to resist the domination of others. He begins to say "I will" or "I won't" and the degree of the negativism in this newly forming personality often varies directly in proportion to the amount of negativistic approach on the part of the parents in their control over their child.

Here, the mother might be advised to remove valuable, breakable objects from the room, as the baby is beginning to walk around. "No, no" must be avoided as much as possible. This is the beginning of the imitative age and a dangerous time when negativism can be encouraged by a negative attitude by the mother. Negativism when associated with the newly developed desire to explore the physical environment often results in trouble for unprepared parents. If a physician counselling parents can anticipate this period and prepare them so that they will not be surprised or have their feelings hurt when it occurs; if he explains to them that the exasperating behavior patterns of the 2- or 3-year-old are not signs of badness or of a problem child but that the child is developing his independence and his mental abilities; if he can help the parents to understand that it is desirable to encourage the child's trend toward independence and self-reliance, although at the same time directing and channelling the child's behavior for his own safety, the child's daily life and the distressed concern of the parents can be made less unsettling. Patience, consistency of management, firmness without domination, and a good sense of humor are keys to emotional approaches which can help parents to cope successfully with this phase of the child's development. Sound advice to parents is: Avoid punishment if possible; it isn't effective. Don't try to be perfect nor have your child perfect. Relax and be natural. Remember, if mother and father are happy, this will be reflected in the child's reactions.

*Early Childhood* (Charts 3 and 4)

It is in the period between 2 to 3 years and 5 to 7 years, when the child remains emotionally dependent upon his parents for his security and many of his social satisfactions, that his physical independence becomes fully manifest. Any extreme feeling of insecurity in relationship to his parents during

CHART 3

**Normal Behavior Patterns of Children Which Appear as or Precipitate Problems for Parents**

| DEVELOPMENTAL AREAS | Age 2½ (30 Months) | 3rd Year | 4th Year | 5th Year |
|---|---|---|---|---|
| MOTOR | | Can now dress alone with easy garments; *not self-sufficient.* | Dress and undress self; not tie shoes yet. | Ties shoes alone; definite handedness; fastens buttons. |
| LANGUAGE | Constant talking. | Stuttering again. (Go easy.) | Lots of silly language. | |
| SOCIAL | Definite preference for mother or father. *Avoid moving homes if can;* don't rearrange furniture; prefers environment static. Everything has its place (go along with it). | Peak of imaginative life. Can tolerate mother's being away—understands she will always return, if so assured. (Day nursery if mother works.) | Temper tantrums and negativism subsiding. Boasts and shows off. Tendency to visit about neighborhood but is not running away. (Good) Let 'em go. | Poised. *Strong sense of pride in possession.* Dogmatic re: own ideas. Self-assertion—even if different from parents. Lies—if frequently, probably "pressured." If angry—stubborn, resistant; whines and pouts—but easily placated with fairness and tact. |
| FEEDING | Beginning to snack between meals. Excessive candy demands. | *Prone to wander around at meals.* Eats better alone—dawdles. | Few problems. May talk so much interferes with eating (be tolerant). | Wiggles lots. Tends to monopolize conversation. Nail biting, nose picking are tension outlets. |
| SLEEP | *Rigid ritual of bed-time; resists naps*—climbs out of bed. Keep bedroom window secured. | A.M. waking problem; wants to get into parents' bed. Likely very upset if wakens and parents not quickly at hand. | Dreams evident (animals ok). Good time to change to junior bed. | Frightening dreams. Select bedtime reading and shows carefully. |
| TOILET HABITS | Boys usually dry now also. | | If still having accidents, wonder why! | Cares for self at toilet. |
| SEXUAL | Confusion and concern over own sex. Need reassurance and chance to discuss their perception of sex differences. | Frequent use of bathroom language. Sex questions begin—satisfy; don't evade. Interest in each other's bodies (not naughty). | | Very interested in babies, (pets), where they come from (don't evade). Awareness and interest in sexual characteristics in others. Modest about self-exposure. Both boys and girls express desire to "have babies" themselves. |
| SCHOOL | | 3½ good time to start school. Accepts suggestion readily. | | Hates "have to rest" naps; otherwise enjoys routine. Adjusts well to school or kindergarten. |

this phase of his development will produce in the child much attention-getting behavior, such as clinging dependence, whining, temper tantrums, refusal to obey—that is, persistence of many patterns of infantile behavior.

Now the child becomes increasingly able to take directions and to conform to social demands. He learns more and more about the rules of authority and the rules of social living. If he loves and respects his parents, the child makes an effort, insofar as he is able, to be like them and to behave as they do.

In addition to learning the elements of family living by his relationship with his parents, the child now begins to develop the capacities necessary for learning to get along with other children. If there are brothers and sisters, he has the opportunity to develop his social feelings with them; if not, he depends upon playmates for this part of his social development. Parents should expect a certain amount of friction between children in early childhood, for at that age they are all self-centered or parent-centered. When a parent-child relationship is satisfactory to them and they feel secure, children are usually able to tolerate and get along with their playmates acceptably. There will be, however, friction, some sibling rivalry and jealousy in any family, and it is the constructive handling and resolving of these frictions and rivalries that lets the child gradually learn about the rights of others and how to share.

Although early childhood is a time when fantasy is very active, children of that age are, at the same time, learning more and more about the realities of the world, although they may yet refuse to accept uncritically the superficial adult answers in regard

CHART 4

**Normal Behavior Patterns of Children Which Appear as or Precipitate Problems for Parents**

The 6th Year—An Age of Tension—Lots of Tension—Time of Many Problems

| | | | |
|---|---|---|---|
| MOTOR | Constantly in motion, but tires easily. Headstrong; clumsy—prone to falls. | SEXUAL | Very interested in marriage and sexual roles; but as to responsibilities, not intercourse.<br>Interested in babies; *reenact baby roles*, i.e., wetting, crawling, putting on diapers, cuddling . . .<br>*Exhibitionistic drives* (don't shame):<br>Boys—show and compare genitalia.<br>Girls—more apt to pull panties off younger children.<br>Frequently play doctor: taking temperature (rectal or vaginal) (after 4-5 good to use oral thermometer in hospital, office). |
| LANGUAGE | Giggly—*frequent use of bathroom terms in calling "names."* | | |
| PARENT-CHILD RELATION. | Beginning to achieve feeling of independence (good). Is at worst and best behavior with mother (ambivalence). Difficult to punish; "take out" on mother (threatens to get another). Begins to realize parents not omnipotent. | | |
| SOCIAL | Scuffling, wrestling and roughhousing. Easily distracted in dressing—dawdles. Is center of universe; must be first; must win, "poor loser"—*will cheat to win.* Lacks self-confidence; apprehensive; needs reassurance and uncritical or patient relationship with parent and teacher. Very sensitive, highly emotional. Marked increase in auditory and spatial phobias: (altiphobia, claustrophobia, firewagons, fireworks, etc.). | SCHOOL | Like school—yet apprehensive and unsure of self; frequently ill till too late to go and quickly recovered. (100% attendance not important.)<br>Embarrassed to ask teacher to go to rest rooms; unable to go to toilet frequently, and fear of accidents leads to fear of going to school.<br>Many children control selves nicely in school then release controls and "hard to handle" when home (again—help parents understand this as needed outlet if they are to conform at school.)<br>High incidence of nail biting, thumb-sucking, chewing on objects as school starts.<br>School discipline often conflicts with permissiveness at home—"hard to take"—child must suppress tension.<br>Marked interest in making and being friends; difficult to maintain as each wants own way in association. (Reassure.)<br>Very "tattle-taley." |
| TOILET HABITS | Probably *occasional "accidents" again*, bowel and bladder—usually afternoons (mostly tension outlet). | | |
| FEEDING | Overeats, stuffs self; *loses all manners.* Is clumsy—grabs, knocks food over and spills; kicks table, tips chair back, etc. Prone to likes and dislikes, but rational about it. | | |
| SLEEP | | | |

to the world around them. There are times when they still prefer their own fantasy as an explanation of questions which arise in their minds.

It is during this period, usually, that a child begins to have feelings and questions regarding sexual matters. He becomes aware of his own sexualities. He probably has discovered the anatomical differences between the sexes, and is now faced with the necessity of accepting his own sexual role in life. This is likely to be marked with great confusion and emotional turmoil in his relationships to his parents and their sexual roles. A little girl, while able to maintain a close identification with her mother, needs also to develop a feeling of satisfaction and confidence in her relationship with her father. This allows her to develop an emotional basis which will eventually help her find satisfaction in her relationship with a member of the opposite sex. On the other hand, a little boy whose chief love object has always been his mother must now begin to identify himself with his father and to think of himself as a man. This may result in a desire to cling to his mother and may precipitate feelings of jealousy and hostility toward his father. Parents often need emotional support as well as the advice of physicians if they are to deal constructively and objectively with sexual feelings and behavior of their children. Being objective about sexual matters is extremely difficult for most parents. As they find themselves confronted with the curiosity and behavior of their children, they often are highly embarrassed, if not anxious, ashamed, or disgusted, owing to their own insecurity in this area. An adult is often inclined to think of a child's sexual interest only from the moral standpoint of the adult, forgetting that in reality it is merely a healthy part of growing up. When children are punished for sexual interest or behavior, or if parents are evasive or give impressions that sexual information is something unpleasing or undesirable, they not only increase the child's need for experimentation, but they also may leave feelings of anxiety, guilt, and hostility in direct association with sexual thoughts. All too often this results in great difficulty in attaining normal heterosexual or marital adjustment later. If the parents can answer a child's questions promptly and honestly, no matter

how early they are expressed, and as simply as possible so that his mental and emotional needs are satisfied, then the child, his curiosities satisfied, can more easily move on to other aspects of learning.[2, 4, 5, 6]

*The Developmental Tasks of Late Childhood*

Late childhood is the age period when a child not only continues to grow up, but also begins to grow out, for it is during this time that the child's interests and activities begin to be centered about the school and the playground. He begins to grow out of the home into community living, and his chief psychological goals now are concerned with school adjustment both academic and social.[8] The child has lost some of his strong emotional dependence upon adults and has become interested in children of his own age. He is looking upon himself as an individual and takes a rather realistic view of his parents, no longer regarding them as omnipotent and infallible. He often demands the right to have his own opinions and to make some of his own decisions; the time of blind obedience to authority is gone. This may be true at school as well as at home. However, as his emotional dependence upon adults has become less imperative, the dependence upon the approval of peers has become stronger. His chief interest in life is now to be one of the group of his own age and of his own sex.

If a child has received enough love and feels secure at home during the infancy and early childhood phases of his development, if he has known the approval of his teachers and has been liked during his first experiences in school, he is now ready and able to give both love and affection to friends in his play groups, and also to his parents, even to brothers and sisters at times. Truly this ability to give affection as well as the need to receive it is a big step toward maturation and emotional development of the child. It is when he has not received such love in the past that he may be handicapped in developing a mutually satisfactory relationship with his peer group and with adults.

It is often in late childhood that the pressures from the parents to "do well" or "to do better than" cause conflict and trouble. It is wise to caution parents to be sure they are not expecting more of the child than his ability can deliver.

In group activities, children learn more about the rights and rules of social living. As the child develops the ability to read and write, the use of language to exchange ideas and to influence other people comes into its own. He becomes increasingly interested in the why and wherefore of things as he faces problems and begins to develop physical skills.[8] He can now accept chosen or delegated tasks, and if he is helped to accomplish these, thus winning approval for his achievements, he acquires the habits of industry, a feeling of self-confidence and adequacy upon which can be built a successful and productive life.

As school attendance is the first big step into community living, it seems obvious that well child conferences should not be discontinued until the child has satisfactorily and happily made this transition from the home into community living.

*Adolescence*

The problems of adolescence are of great complexity. The importance and responsibility of pediatricians to the adolescent is great because of the varying rates of maturation in different children. No specific limits can be set, but rather (again emphasizing the individuality of the child) one must be thoroughly aware of the developmental patterns of childhood in order to determine when a child has achieved and passed through adolescence, and thus accomplished all the developmental tasks of childhood.[8]

## THE PHYSICIAN'S ROLE IN EMOTIONAL PROBLEMS

The question arises, what kinds of psychosomatic or emotional problems can a physician in general practice or a pediatrician be expected to deal with effectively? Obviously this will vary somewhat with the individual practitioners and their own feelings, but it seems logical that most of the problems appearing in the first six years of life can be dealt with by them. This is a habit training period, and the points of conflict are actually normal developmental patterns of behavior, although often misinterpreted as "problems" by parents and physician. It is conflicts of this order that can so easily be avoided if foreseen or "nipped in the bud" by preparing the mother for them in advance, and by reassuring over-concerned mothers or fathers that such and such is to be expected at this age; for the child, it is normal behavior.[7] A physician's task may be mainly to help parents accept their child as he is.

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# Advances in Pediatric Surgery

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▪ *Recent advances in pediatric surgery have been made in several fields. Hydrocephalus is again being treated by draining the cerebrospinal fluid into either the ureter, the mastoid antrum or the peritoneal cavity. Funnel chest should be corrected surgically. Congenital atresia of the esophagus is best treated by a one-stage operative repair. Patent ductus should be closed. Operations are available for cyanotic children. Intussusception is again being treated by barium enema in selected cases. Megacolon can be benefited by surgical procedures, which now are directed at the distal spastic segment rather than the proximal dilated segment.*

MANY OF THE ADVANCES in the field of pediatric surgery stem indirectly from increased knowledge and ability to cope with the fundamental problems of hemorrhage, shock, electrolyte losses, infection, and anesthesia. The theoretical concepts, which are common to medical as well as surgical pediatric problems, are rather difficult to implement in children, particularly in newborn infants, and certain practical advances have been made in recent years which are worthy of emphasis. These practical considerations pertain to the administration of anesthesia and parenteral solutions.

Endotracheal anesthesia in infants was occasionally followed by obstruction to the airway from edema and irritation. This may still occur, but is becoming rare now that small endotracheal catheters of inert plastic material have been developed for endotracheal intubation of infants. Similarly, the control of the flow of respiratory gases through endotracheal tubes has been facilitated by the use of non-resistance valves (Slater valves). The value of bronchoscopy and its use in aspiration of the tracheobronchial tree for the prevention and treatment of atelectasis has become available for newborn infants with the development of a bronchoscope and laryngoscope (Michelson[10]) especially for infants.

The best treatment of shock is prevention, and the simplest manner of preventing fluid, blood, and electrolyte loss during major surgical procedures in infants is to insert a small polyethylene catheter into the internal saphenous vein. This is an extremely valuable procedure which can be done very simply under local anesthesia. It may be done while the child is being prepared for operation or during anesthetization immediately before operation. A transverse incision 1 cm. in length is made in the skin just anterior to the internal malleolus. The subcutaneous fat is separated bluntly in the direction of the internal saphenous vein until the vein is identified. The vein is ligatured distally, an incision made into it, a plastic catheter or a blunt-needle cannula inserted, and passed upward into the saphenous vein for a few inches. The cannula is tied in place, and a single suture closes the skin wound. It should be remembered that as it is difficult or impossible to draw blood back freely in newborn infants, the best way to make sure the indwelling catheter is functioning is to drip fluid into the vein. The catheter may be used for continuous drip infusion in the postoperative period for several days. This simple and satisfactory method of parenteral intubation is a significant advance in pediatric surgery and may prove life-saving.

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## NEUROSURGICAL ADVANCES

The surgical treatment of hydrocephalus has occupied the interest and attention of pediatricians and surgeons alike. Hydrocephalus may be related to a block in the free circulation of the cerebrospinal fluid, either on a congenital, traumatic, or postinflammatory basis; or it may result from failure of absorption of the cerebrospinal fluid. Diagnostically, dye studies and air studies to determine the type of hydrocephalus are particularly important, for upon the diagnosis depends the kind of surgical procedure to be employed.

*Torkildsen's Procedure.*[15] The Torkildsen procedure consists in inserting a rubber catheter or polyethylene tubing into the posterior horn of one of the lateral ventricles, passing the tubing beneath the bone but outside the dura, and implanting the other end into the posterior cistern. It is also possible to pass the shunting tube subcutaneously. This shunt relieves an obstruction to the intracranial flow of cerebrospinal fluid, and is applicable to tumors of the pineal gland, third ventricle, aqueduct, or fourth

ventricle. It also by-passes a congenital stenosis of the aqueduct of Sylvius. It requires a normal posterior cistern and a normal absorption of cerebrospinal fluid once it has gained access to the posterior cistern. It is not applicable, therefore, to the obstructive hydrocephalus often associated with spina bifida, which is generally owing to an accompanying Arnold-Chiari malformation.

*Matson Procedures.*[8] In 1951 Matson reported the successful use of two procedures in hydrocephalus, the choice between them depending upon the presence or absence of a block to the free flow of cerebrospinal fluid:

1. *Anastomosis between the lumbar subarachnoid space and the ureter.* If no obstruction exists to the flow of cerebrospinal fluid, as in the communicating or idiopathic hydrocephalus, a shunt can be established between the lumbar subarachnoid space and the ureter. This consists in sacrificing one kidney, using a small polyethylene tube to bridge the gap, and connecting the lumbar subarachnoid space to the ureter.

2. *Ventriculo-ureterostomy.* In patients who have an obliteration of the spinal as well as the intracranial surface subarachnoid spaces the previously described shunting procedures would be useless. Matson,[9] therefore, has elected to shunt the cerebrospinal fluid directly from the ventricle into a ureter by means of a long subcutaneously-implanted polyethylene tube. The procedure seems indicated in hydrocephalus of the following types:

(1) Obliteration of the absorptive surfaces for the cerebrospinal fluid, as an aftermath of purulent meningitis or diffuse hemorhage into the subarachnoid space. Many more patients survive purulent meningitis nowadays with antibiotic therapy, and obliteration of the posterior cisterns and subarachnoid absorptive pathways is more frequently encountered.

(2) In benign obstructions of the aqueduct of Sylvius or posterior fossa, either on a congenital basis or from Arnold-Chiari malformation. The subarachnoid pathways may also be obliterated or may not have developed. In such circumstances, ventriculo-ureterostomy offers relief from progressive hydrocephalus.

In young children the obvious problem with this procedure is that of subsequent growth. The consequences of this difficulty will have to be evaluated in the future.

It should also be emphasized that in the immediate postoperative period problems in fluid and electrolyte imbalance are likely to be troublesome. Attention must be given to chloride, sodium, water and potassium balance.

*Nosik Procedure*[11] (ventriculomastoidostomy). The indications for this procedure are similar to those for ventriculo-ureterostomy. It has the advantage of avoiding fluid and electrolyte loss from the body, for the fluid passes from the ventricle into the mastoid antrum, then into the middle ear and the eustachian tube, and finally is swallowed from the nasopharynx. It also creates a pathway between the ventricle and nasopharynx, a possible route for retrograde infection. In practice, however, the differential pressures and the action of the cilia in the eustachian tube seem to minimize the hazard of retrograde infection.

Briefly, the procedure consists in shunting the cerebrospinal fluid from the lateral ventricle into the mastoid antrum by a small polyethylene tube.

None of the various shunting operations for hydrocephalus is applicable or justified once irreparable brain damage has already occurred. They are not a means of prolonging a demented life.

### THORACIC OPERATIONS

Advances in both techniques and concept of thoracic surgery have been made in recent years. Technical advances have permitted the surgical repair of such conditions as funnel chest, atresia and stricture of the esophagus, patent ductus arteriosus, coarctation of the aorta, ringed aorta, and anomalous subclavian vessels. Conceptual advances have resulted in the use of operations to alter the flow of blood through the lungs; and cyanotic heart disease, pulmonary stenosis, and transposition of the great vessels have become amenable to surgical benefit.

*Funnel Chest.* The cause of funnel chest is still not clear, but it is related to a short central tendon of the diaphragm in infancy and in later years to a progressive deformity in the growth of the sternum and attached costal cartilages. Surgical correction is advisable in order to correct the deformity, which becomes of psychological concern to a growing child, to prevent progressive increase of the deformity with attendant kyphosis and rotation of the sternum and costal structures, and to relieve cardiac and pulmonary embarrassment which may occur in later years from compression of the heart or lungs.

It is not possible to predict the rate of progression of the deformity. In general, the earlier surgical correction is initiated the simpler the surgical procedure required. In cases of long standing, with severe deformity in adolescence, extensive operation may be only partially corrective.

In young infants and in children under two years of age the most commonly used surgical procedure is to section the attachment of the central tendon of the diaphragm to the xiphisternum after excision of the xiphoid process. The subcostal ligament is

also incised and the sternum elevated. The release of the abnormal pull of the diaphragm on the sternum permits elevation of the sternum and prevents or retards subsequent progression of the deformity with the attendant costal arch deformity. In older children, or in adolescents, it is generally necessary to excise all the deformed costal cartilages and ribs anteriorly from the second to the seventh inclusive, mobilize the sternum from the anterior mediastinal structures, osteotomize the sternum at the sternomanubrial junction, and then maintain the sternum in an elevated position until healing has occurred either by suturing the sternum to the manubrium in the corrected position or by using a long rib strut beneath the sternum to maintain proper elevation.

*Congenital Atresia of the Esophagus.* The commonest type of congenital atresia of the esophagus, which results from a failure of proper embryonic separation of the esophagus from the tracheobronchial tree, is as follows: The upper end of the esophagus terminates as a dilated blind sac about the level of the first to second thoracic vertebrae, and the lower end of the esophagus, which is thin and undeveloped, communicates with the trachea through a tracheo-esophageal fistula. In former years it was possible to reconstruct the defects by employing staged operations and eventually obtain continuity of the upper alimentary tract by an antethoracic cervical esophagogastrostomy. This entailed months of hospitalization, often with a distressing result from the parental viewpoint, even if the child survived. The brilliant advances in thoracic surgery in infants in recent years now permit a one-stage reconstruction of this disorder by direct repair of the tracheo-esophageal fistula and a simultaneous end-to-end anastomosis of the esophageal segments. A normal anatomical and physiological alimentary tract is established. The mortality rate from the procedure is less than 50 per cent, taking statistics the country over. The sooner operation is performed, the less likelihood of attendant, oftentimes fatal, complications from pulmonary infection, dehydration, and malnutrition. It is imperative, therefore, that the condition be recognized early. Inability to swallow, respiratory distress and cyanosis on feeding, and the spilling over of food or saliva into the tracheobronchial tree are symptoms. The diagnosis may be readily confirmed by inability to pass a catheter down the esophagus and by roentgen studies made with Lipiodol® to outline the upper blind sac of the esophagus. The presence of air in the intestinal tract establishes the presence of a tracheo-esophageal fistula in association with the upper blind esophageal sac.

The author's preference is for right transthoracic extrapleural repair with resection of a segment of the fourth rib. In this procedure the lower end of the esophagus is disconnected from the trachea, the tracheal fistula repaired, and a primary end-to-end anastomosis of the esophageal segments is done. Gastrostomy is established for feeding until adequate food can be taken orally.

*Stricture of the Esophagus.* Congenital complete atresias of the esophagus can be repaired by antethoracic cervical esophagogastrostomy. When the patient is older it is possible to drop the antethoracic stomach back into the thoracic cavity to improve the cosmetic result. Localized congenital strictures or diaphragms of the esophagus can be repaired by transthoracic resection of the esophagus with primary end-to-end anastomosis of the esophagus. Extensive strictures can be corrected by resection of the strictured area and intrathoracic esophagogastrostomy, a procedure that entails sacrifice of the cardiac sphincter and may be followed by peptic esophagitis.

The commonest strictures of the esophagus, however, result from trauma—usually from swallowing of a caustic material such as lye. In recent years the armamentarium for management of such lesions has been enhanced by the development of the Tucker[16] indwelling dilators and the Hurst mercury bougies. Once satisfactory dilation of the stricture has been obtained, the patient or the parents can be taught the use of the Hurst mercury dilators to maintain the esophageal lumen.

*Patent Ductus Arteriosus.* Patent ductus arteriosus was the first congenital lesion of the great vessels to be treated successfully, and universal experience since 1938 has attested the success and safety of the operation first performed by Gross.[4] A child in whom the condition exists may appear to be normal, or he may be underdeveloped. A palpable thrill over the precordium and a continuous, harsh "machinery" murmur of an arteriovenous fistula, heard best over the second and third interspaces to the left of the sternum, are characteristic. There is greater than normal disparity between systolic and diastolic blood pressure, with the diastolic pressure low. As much as 70 per cent of the blood may be shunted through the ductus back into the lungs, and in x-ray studies an enlargement of the pulmonary conus and increased vascular markings in the lung fields may be noted.

If a ductus does not close by the age of two years operation should be advised, for the period in which operation can be most easily and safely accomplished is between two and six years of age. The surgical procedure consists in division of the ductus, if this can be performed safely; or, if the ductus is so short and broad that division seems unsafe, multiple suture ligatures may be used with only a rare recurrence.

*Coarctation of the Aorta.* The diagnosis of coarctation of the aorta is ordinarily not difficult, if the condition is suspected. Nosebleeds, headaches, cold legs, pains in the extremities, and easy fatigability on running should arouse suspicion of this lesion. Hypertension in the upper extremities with femoral pulsations and pressure diminished or impalpable affords a clinical diagnosis, which can be verified by roentgenographic observation of notching of the ribs and left ventricular hypertrophy. There are two common types: (1) the adult type, in which the constriction is short, and in which resection of the coarcted area with end-to-end anastomosis of the vessel is feasible; and (2) the infantile type, in which the coarcted segment is long and irregular, oftentimes with a patent ductus arteriosus entering below the coarctation, and in which direct repair of the aorta is not possible.

Crafoord[3] and Gross[5] described the successful repair of coarctation of the aorta in patients by direct end-to-end anastomosis. The pertinent remaining questions as to growth of anastomosed vessels after circumferential suturing and as to the technique of bridging aortic defects have been partially answered in recent years. It has been observed that the size of an anastomosed area increases somewhat with the size of the patient, particularly if the suture line is interrupted in several places in its circumference. Aortic defects have been bridged by direct substitution of specially preserved aortic homografts (Gross[6]), and other investigators have circumvented the problem by swinging the left subclavian vessel down to bridge the gap and carrying out anastomosis between it and the aorta.

As there is little likelihood that coarctation will cause serious damage before the age of six years, the optimum age for operation seems to be between six and fifteen years. As three-fourths of patients with coarctation of the aorta die in early adult life, operation before age fifteen is advisable.

*Anomalous Subclavian Artery and Ringed Aorta.* Anomalies of the arch of the aorta are not uncommon, but not all of them cause symptoms. Symptoms, if they occur, are related to respiratory or esophageal obstruction. Difficulties in swallowing or repeated bouts of dyspnea, respiratory distress, or coughing should arouse suspicion of these lesions, particularly if other congenital anomalies exist. The diagnosis is confirmed by x-ray visualization of compression of the esophagus. The two commonest anomalies of the arch are ringed aorta and aberrant right subclavian artery. In repair of ringed aorta the smaller aortic arch is divided and the ends sutured. Anomalous right subclavian artery is corrected by dividing the artery just distal to its origin from the descending aorta and permitting it to retract to the right of the trachea and esophagus.

*Cyanotic Heart Disease.* Congenital heart disease is commonly divided into the cyanotic and acyanotic groups. Any condition which permits shunting of blood from the right side of the heart to the left, or which prevents an adequate flow of blood through the lungs will result in incomplete saturation of the arterial blood. Cyanosis results, or rather is "visible," when the amount of oxygen-deprived hemoglobin in blood circulating in the "visible" capillary beds (lips, fingernails) is 5 gm. or more per 100 cc. In children, cyanosis from failure of blood to be oxygenated as it passes through the pulmonary bed is rare, and the common cause of cyanosis is from venous admixture. The common cyanotic lesions which have become amenable to surgical benefit are:

1. *Tetralogy of Fallot:* The four characteristics of this anomaly are pulmonary stenosis, interventricular septal defect, dextroposition of the aorta which overrides the septal defect, and hypertrophy of the right ventricle.

A patient with this condition is cyanotic, and in x-ray films of the chest diminished pulmonary artery markings and right ventricular enlargement may be observed. The general principle of surgical treatment is to increase the amount of blood flowing through the pulmonary circuit. In infants, creation of this life-saving artificial ductus is best accomplished by direct anastomosis of the aorta to the pulmonary artery, the Poth-Smith operation.[12] In children over two years of age the Blalock-Taussig operation[1] is preferable, namely, anastomosis of the subclavian artery to the pulmonary artery. The optimal age for the operation seems to be between the ages of five and ten, but it may have to be done earlier if life and development are unduly threatened at an earlier age. "The sicker the sooner" is the accepted motto.

Some day it may be possible to deal with the problem more directly by surgical enlargement of the stenosed portion of the pulmonary artery, but this must await further refinements in angiocardiography to permit better visualization of the existing anomalies and a greater experience with the technique of Brock[2] for direct valvulotomy. It is probable, however, that the direct method would not be applicable if the stenosed portion was long, but if it was short and diaphragm-like and the pulmonary artery beyond it was enlarged, direct operation probably would increase the flow of pulmonary blood without adding another cardiovascular anomaly.

2. *Stenosis of the pulmonary valve.* This condition is statistically one-tenth as common as the tetralogy of Fallot. It is accompanied by cyanosis in 70 per cent of cases because of accompanying interauricular septal defect or interventricular septal defect with a right-to-left shunt. Dilation of the pulmo-

nary artery beyond the point of stenosis, which is characteristic, may be observed on a plain film of the chest or angiocardiographically. Right ventricular pressure is very high, and the right ventricular hypertrophy observed at operation is striking. If the pulmonary artery is palpated at a point immediately beyond the site of stenosis, the spurting of the jet-like stream of blood through the stricture can be felt. Creation of an artificial ductus in this situation may initiate right-sided heart failure. The operation of choice is the Brock procedure,[2] in which the pulmonary valve is cut and dilated through the use of special valvulotomes and dilators passed through a small incision in the right ventricle.

*Other Less Common Anomalies.* Surgical possibilities are being explored in the management of complete transposition of the aorta and pulmonary vessels and in the treatment of tricuspid atresia. Results in these conditions are still quite unsatisfactory. Similarly, the closure of interauricular and interventricular septal defects awaits the development of suitable pump-oxygenators which will sustain both cardiac and pulmonary functions while intracardiac operation is being carried out.

#### ABDOMINAL OPERATIONS

*Intussusception.* In recent years there has been a renewal of interest in nonoperative management of intussusception. The majority of cases of intussusception occur in infants under two years of age, and rarely is a local lesion such as a polyp, tumor, Meckel's diverticulum, or ectopic pancreatic nodule encountered. Intussusception generally begins at the ileocecal valve, and as the intussuscepted bowel drags more of the enveloping loop in after it, the head of the intussuscipiens remains constant. The most characteristic symptom is discharge of blood into the bowel owing to the vascular embarrassment of the intussusceptum. Edema and compression narrow the lumen of the bowel, causing first partial and later complete obstruction. Gangrene of the bowel occurs after a variable period of time, depending upon the degree and completeness of vascular occlusion. Oftentimes a sausage-shaped mass is palpable in the left upper quadrant of the abdomen and there is absence of bowel in the right lower quadrant. Colic and vomiting, blood in the stool or discharge of bloody material, partial obstruction, and an abdominal mass occur early; later, ileus, peritoneal irritation, and manifestations of toxicity appear. The diagnosis is confirmed by roentgen examination after barium enema.

In clinical and experimental observation[13] it has been noted that barium introduced under hydrostatic pressure of three to three and one-half feet will usually reduce non-gangrenous intussusception but will not reduce gangrenous intussusception nor risk rupture of the intussuscipiens or intussusceptum. Accordingly, conservative management consists in inserting a Foley catheter into the rectum, holding the buttocks together, and running in barium under hydrostatic pressure of three feet. If complete reduction of the intussusception occurs, the intussuscepted loop will disappear and barium will break through the ileocecal valve into the terminal ileum. No further treatment is then necessary, and recurrence of the intussusception is extremely rare.

If the intussusception cannot be reduced by hydrostatic pressure with barium, or if any doubt exists as to the completeness of the reduction, or if there are continuing symptoms of peritoneal irritation to cause suspicion of the viability of the intussuscepted bowel, immediate laparotomy is indicated. This can ordinarily be accomplished through a McBurney or short transverse right-sided incision.

*Hirschsprung's Disease* (megacolon): Concepts of the cause and treatment of megacolon are in process of revision, and the condition is no longer regarded as an idiopathic dilation of the colon. Formerly, cases in which intestinal dilation and severe constipation were present and in which a tremendously dilated colon with poor haustral markings was observed in roentgen studies with barium enema were grouped as "idiopathic megacolon." It now seems better to divide such cases etiologically:

1. *Achalasic or aganglionic megacolon* (true Hirschsprung's disease). In this condition the parasympathetic ganglion cells of the myenteric plexus are absent. The aganglionic area, usually the lower rectum and the sigmoid colon, is narrow and spastic. The colon is greatly dilated above the aganglionic segment. Usually the anus and terminal rectum are normal.

2. *Functional megacolon.* In megacolon of this classification, the colonic dilatation is secondary to functional obstruction in the bowel. The origin of this functional obstruction may be dietary, psychologic (improper bowel training), endocrinologic (hypothyroidism and cretinism), or pain and spasm from an anal fissure.

3. *Organic megacolon* is that which is caused by an anal stricture, by inadequately repaired anal atresia, or by extrinsic or intrinsic bowel tumor that mechanically obliterates the lumen of the bowel.

In functional and organic megacolon the cause is apparent and the treatment is to eliminate the cause.

As to aganglionic megacolon, data obtained through pathological examination of the diseased segment and results of studies of physiological pressure with intracolonic balloons have led to a changed concept of therapy. Whereas previously the dilated

segment was looked upon as the diseased segment, and was resected (oftentimes after a preliminary colostomy proximally), nowadays attention is directed to resecting the aganglionic distal narrow segment as a means of relieving the megacolon. Svenson[14] and Hiatt,[7] both advocates of this concept, have developed a sphincter-saving operation which permits resection of the diseased aganglionic segment with preservation of the anus and its sphincter. In that procedure the ganglion-containing dilated portion of the bowel above the resected narrowed segment is brought down through the anal sphincter and sutured to the anal mucosa. Further time will be necessary to evaluate late results, but the immediate results have been highly satisfactory.

It is worthy of emphasis that this operation is applicable only if the megacolon is of aganglionic type. Diagnosis of this condition is best established by noting the onset of obstructive symptoms, which is invariably at birth or within the first few days thereafter. The narrow obstructed rectosigmoid is best visualized roentgenographically in oblique films taken after the large redundant sigmoid colon has been manipulated out of the pelvis with the patient in the Trendelenburg position. Svenson emphasized that, since many patients with aganglionic megacolon also have an atonic bladder, cystometrograms with residual urine determinations are advisable preoperatively.

Once the diagnosis of true congenital megacolon has been made, operation should be considered if the roentgenographic characteristics are present or if the disease is progressive. For extremely sick patients, preliminary colostomy may be necessary; otherwise, a one-stage procedure is safe and satisfactory.

How some patients with megacolon were cured previously by resection of the dilated segment is subject for speculation.

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# Treatment of the Nephrotic Syndrome

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*• The nephrotic syndrome may be due to varied cause. It may end fatally or in complete healing. No specific cure exists as yet, and basic treatment is dietary. The degree of edema does not necessarily hold a direct relationship to the status of the kidneys or to the eventual outcome.*

THE NEPHROTIC SYNDROME is a disease state characterized by edema, hypoproteinemia, lipemia, proteinuria, and perhaps evidences of a degenerative renal lesion in the urinary sediment. Its etiologic delineation is varied, and often cannot be determined. The syndrome may take place as a consequence of glomerular nephritis when this disease enters the degenerative stage, and it has been seen in association with amyloidosis. It is thought to occur sometimes as a "hypersensitivity reaction" to a variety of stimuli, the terms lipoid nephrosis, pure proteinuria and prerenal proteinuria having been used to describe this condition, which occasionally may be cyclic.[1,2,3,7,9] Rytand[12] described patients in whom the nephrotic syndrome was associated with poison oak dermatitis. The author has observed patients in whom it seemed to be induced by the administration of gamma globulin to ameliorate rubeola, by multiple insect bites, by therapy with penicillin and by the use of sulfonamides.

While the nephrotic syndrome occurs most frequently in childhood, it may occur at any age. In some cases the disease may terminate fatally, but in a substantial number it may disappear and eventually heal completely. This difference in outcome is unexplained, but it does not appear to depend entirely upon the cause of the disease.

No specific cure for the nephrotic syndrome exists as yet. For reasons given in detail elsewhere[2,4,5,8,10] the author believes that necessary treatment consists of maintenance of a large fluid intake and the use of a calorically sufficient diet containing a minimum but adequate amount of protein. For adults, this minimum adequate amount of protein has been shown by the careful studies of Sherman and his associates[13] and by Hegsted and co-workers[6] to be no more than 0.5 gm. of protein per kilogram of body weight. To this amount of dietary protein should be added an increment equal to that excreted in the urine. So far as the author knows, the actual minimum adequate amounts of protein necessary for children have not been established; the usual estimates of 1.5 to 2.5 gm. of protein per kilogram of body weight may well be excessive. In the Clinic for Renal Disease of the Stanford University Outpatient Department, for some years children with renal disease have been treated with calorically adequate diets containing from 0.75 to 1.0 gm. of protein per kilogram of body weight to which has been added an amount equal to that lost in the urine. No deleterious effects upon their growth or development have been observed. Daily rations of calcium and vitamins are given as dietary supplements.

Variations from day to day in the amount of subcutaneous edema are not necessarily prognostic, for they do not always reflect parallel changes in the status of the kidneys or in the fundamental disease process. Treatment to control the edema consists mainly of sodium restriction. In general, the daily intake of sodium chloride must be reduced to less than 1.0 gm. The use of certain currently available ion exchange resins to diminish the gastrointestinal absorption of sodium has not been helpful for the treatment of children with the nephrotic syndrome in the author's experience.

If fluid accumulation increases despite efforts to control it through dietary sodium restriction, it may be evacuated. It may be withdrawn from the chest and abdominal cavities by paracentesis. Southey tubes are helpful for removal of large subcutaneous accumulations of fluid in the lower extremities. In certain instances, the administration of corticotropin (ACTH), cortisone or salt-poor human albumin solution may be of value. Some patients treated with corticotropin or cortisone may experience remissions for varying periods. Mercurial diuretics should not be used to remove fluid since they are nephrotoxic and since they are not as a rule effective in conditions like the nephrotic syndrome which are associated with heavy proteinuria.

While anemia of some degree often accompanies the nephrotic syndrome, it is usually asymptomatic and requires no treatment other than insuring an adequate dietary intake of iron and vitamins. Attempts to correct it through the use of iron, liver,

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$B_{12}$ or other hematinic substances have not been successful. If the patient becomes too weak and fatigued for his general needs and comfort, blood transfusions are helpful. The beneficial effect is transient, however, and once begun they often must be repeated to maintain symptomatic relief.

The use of watermelons and watermelon juice for treatment of the nephrotic syndrome recently has had considerable popularity among certain patients and has been widely publicized. Aside from being a novel and pleasant source of fluid, watermelons are of no proven value in the treatment of this condition.

Patients with the nephrotic syndrome are particularly vulnerable to infection. Peritonitis occurs rather frequently, and it was a principal cause of death before antibiotic agents were available. While it is not intended to suggest that all febrile illnesses in these patients should be treated indiscriminately with antibiotics, such drugs should be used without delay and in as specific a manner as possible when it seems likely that the illness is of bacterial origin. If possible, appropriate cultures to determine the particular organism involved and its antibiotic sensitivities should be obtained *before* treatment is begun. Certain patients appear to be more prone than others to peritonitis, and in some of them one bout follows another with perhaps no more than a few weeks intervening. Small daily prophylactic doses of a broad spectrum antibiotic have been used with success in preventing or in diminishing the frequency of these attacks.

Some patients with pronounced edema and abdominal distention from ascites have repeated episodes of febrile illness associated with abdominal pain and tenderness. Initially the symptoms and signs closely mimic those of acute bacterial peritonitis, but disappear completely in one to two days even without treatment and the ascitic fluid remains sterile. On careful examination a thrombosed vein may be noted in the abdominal wall, with an accompanying streak of erythema contrasting with the pallor of the swollen, edematous abdomen. The tenderness may be more pronounced in the affected area than over the rest of the abdomen, and at times the thrombosed vein may be palpated as a tender cord. These clinical observations have been confirmed by pathological examination. While this condition is transient and requires no treatment, it is so closely similar to acute bacterial peritonitis that antibacterial therapy must be instituted without delay and continued until fever disappears and the situation is clarified.

A hopeful attitude should be maintained, particularly with children.[11] Parents should be warned against showing anxiety, for psychologic problems in these children often stem from this cause. For the same reason, the dietary principles outlined previously should be incorporated easily into the family mealtime routine. Children with the nephrotic syndrome should be treated as normally as is possible. They should attend school, they should play with other children, and they should be taught to consider the edema as a temporary hindrance which can be controlled and tolerated rather than as a symbol of sickness and disease.

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# Feeding Premature Infants

## Recent Modifications in the In-Dwelling Nasogastric Tube Method

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*• In a two-year period some 600 premature infants were fed through an in-dwelling plastic nasogastric catheter. The results suggest that this method is practical and less fatiguing than gavage or dropper feeding. To increase the ease and safety of this procedure certain modifications in the technique of taping the catheter and of preparing its leading end are suggested.*

USE OF polyethylene nasogastric tubes for the feeding of premature infants has now had a two-year clinical trial. The method has been used in more than 600 cases. Originally developed to eliminate the factor of feeding fatigue in weak premature infants, it has proved a practical alternative to the more exhausting gavage and dropper methods. Often a premature infant who becomes cyanotic when attempt is made to pass a gavage tube will sleep throughout the feeding period when a nasogastric tube is in place, and can be fed, without distress, at any interval desired by the physician.

Extensive use of this method by several pediatric centers* has allowed comparison with other feeding procedures and has led to certain important modifications in technique. Answers to some of the problems that arose concomitantly with widespread use of the plastic catheter have been provided. More detailed information is now available on the relatively minor questions of the best method of taping the tube in place and the length of time the tube should remain in one nostril, as well as on the major questions of esophageal irritation, gastric perforation, and the possibilities of tracheal instead of esophageal intubation.

The indications for the in-dwelling nasogastric tube remain as originally described.[3] It is designed only for those infants who are too weak to suck well, and those who become cyanotic with gavage or dropper feedings. The tube may be inserted with a minimum of disturbance to these babies, and once in place it may remain for as long as twelve days before it is necessary to change it to the opposite nostril, and in the esophagus for as long as 65 days. Usually it is not necessary to feed by this means for so long a time. As soon as the baby begins to gain weight and strength, frequent attempts should be made to start nipple feedings, and once the baby is able to take adequate amounts in this fashion the tube should be withdrawn.

The method of taping the tube in place has occasionally caused difficulty. A premature infant who is too weak to suck is often surprisingly adept at prying loose any exposed portions of the tube. As was suggested in the original communication,[3] a "generous amount" of adhesive tape should be used. To avoid sharp turns in the tube, it should be held in place in a sweeping curve from the nostril to the opposite cheek, and thence to the temporal region (Figure 1). Standard adhesive tape applied in liberal amounts usually is only temporarily and mildly irritating to the skin of the baby. Owing to the high humidity maintained in the units in which most premature infants are kept, plastic tape seldom serves the purpose.

Now and then a baby dislodges a tube despite firm taping. Several times in the author's experience the tube was swallowed and appeared in the feces some few days later. As a precaution, therefore, an overhand knot should be tied in the exposed end of the tube, and the knot then taped to the baby's forehead (Figure 2).

The factor of esophageal irritation is difficult to evaluate. Results of observations thus far suggest that it is not a prominent feature. In no instance has

Figure 1

Presented as part of a Panel Discussion on What's New in Pediatrics before the Section on Pediatrics at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

*Babies Hospital, New York City; Children's Hospital, Cincinnati; Charity Hospital, New Orleans.

Figure 2

death been attributed to ulceration, and the incidence of ulceration associated with this method of feeding apparently is not inordinately high. (Gruenwald and Marsh[2] reported ulceration in 16 2/3 per cent of 310 infants who had not had esophageal intubation.) Although there is no direct evidence that the incidence of ulceration is related to the duration of intubation, certainly the shortest possible period is to be desired.

Although gastric perforation is a rare concomitant of feeding by the method under discussion, it is an extremely important consideration. Apparently there are at least two pertinent factors: the size of the tube, and the method of preparing the leading end. Use of a tube with an internal diameter larger than .07 cm. (external diameter equivalent to No. 3 French catheter) increases the likelihood of gastric perforation. Two instances of the occurrence of perforation under these conditions have been reported. It is not necessary to use the larger tubing, since most milk preparations will pass fairly easily through the No. 22 or No. 23 needle that is inserted into the tubing. Originally it was suggested that the end of the tube be cut square and smoothed with fine emery paper; but even thus prepared the leading end can still be hazardous, and to reduce the danger the tip may be sealed with a coating of paraffin and then an elliptical side opening made in the tubing just above the paraffin plug. Cutter[1] recently suggested a valuable modification: If, instead of paraffin, a small bubble of Duco liquid cement is allowed to dry on the tip, a perfectly smooth and durable leading edge that is non-irritating to the gastric mucosa is formed.

Although there is always the dangerous possibility the tube may be introduced into the trachea rather than into the esophagus, thus far there has been no problem in this regard. Often an infant's first reaction to the entering tube is an attack of sneezing, and occasionally coughing, but there is little respiratory distress. The sneezing often continues for several minutes, but thereafter the infant appears to have little awareness of the tube. To make sure that the tube is correctly placed, 1 cc. of air should be injected through the tube and the sound of air entering the stomach listened for with a stethoscope over the abdomen. As a final check 0.25 cc. of saline solution should be infused and the infant watched for signs of respiratory distress.

This method of feeding is not entirely without hazard, and despite its apparent advantages over older methods it cannot be used as a substitute for skilled nursing care, nor simply as a convenience to the staff.

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# California Encephalitis Virus

## A Newly Described Agent

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### Part I.* Evidence of Natural Infection in Man and Other Animals

*• In three cases of encephalitis in humans that occurred in the area where the newly described California virus was isolated from mosquitoes, serological evidence seemed to indict the California virus as the etiological agent. In the case of an infant with very severe disease, the serological evidence was convincing; the evidence was almost as strong in the case of a seven-year-old boy; the results in an adult were equivocal.*

*Inapparent infection in man is quite common as indicated by neutralization tests on the sera of nearly 600 residents of California, but encephalitic manifestations of infection are extremely rare. In Kern County, California, where the virus was discovered, approximately 11 per cent of the population has been infected. Infection rates are higher in adults than in very young children.*

*Absence of neutralizing antibodies from 64 specimens of blood from persons in Japan, Washington, and other states supports the specificity of the neutralization test in man and suggests that this virus is absent or is not being similarly transmitted in some areas.*

*Serological evidence from serial bleedings of two sick horses suggested, but did not definitely establish, that this virus leads to a naturally acquired encephalomyelitis in horses. Serological tests with the viruses of western equine and St. Louis encephalitis did not lead to any other etiological diagnosis in the sick animals studied.*

*Results of neutralization tests on the sera of eight horses and three cows in Kern County suggested extremely high infection rates, and an immunity rate of 18 per cent was noted in rabbits and ground squirrels. In the natural biological cycle rabbits and ground squirrels are suspected as the possible counterpart of birds in the St. Louis and western equine virus cycles. There is no evidence from field or laboratory to indicate that birds become infected with the California virus.*

*Sera from 33 mammals other than man were collected from Northern California and Washington. All were free from neutralizing antibodies, again supporting the specificity of positive findings from Kern County.*

A NEUROTROPIC VIRUS, which was named the California virus,[3,7,8] was isolated in 1943 and 1944 from three separate pools of mosquitoes† from Kern County, in the San Joaquin Valley of California. This virus was not found to be related to any other virus discovered and described previously, with which it was compared. The California virus is apparently a new member of the rapidly growing family of arthropod-borne encephalitic viruses. The isolation, identification and description of its biological properties are presented in another paper in this series.[9] This virus is pathogenic by intracerebral inoculation to mice, hamsters and cotton rats, and also multiplies in embryonated hen's eggs. The clinical and pathologic manifestations in laboratory animals resemble those produced by the arthropod-borne encephalitic viruses endemic in the same valley area—the western equine encephalomyelitis and the St. Louis encephalitis viruses. The virus multiplies and circulates in the blood of rabbits and ground squirrels, after peripheral inoculation, although the animals remain free from obvious signs of infection. Thus, the agent is presumably available in nature for mosquito infection. In the laboratory, mosquitoes have been infected and by their bite have transmitted the virus.[10]

#### CLINICAL DISEASE IN MAN

Since the first California virus strain (BFS 91) was isolated and identified in 1943, evidence of clinical disease in man has been sought. Because the virus produced encephalitis in certain laboratory animals and apparently has so many characteristics of the arthropod-borne group of encephalitis viruses it seemed reasonable to look for it, by serological tests or isolation methods, as the cause of clinical encephalitis in man. As will be pointed out, sero-

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*Parts II and III are appearing in another journal.[9, 10]

†Isolated from two pools of *Aedes dorsalis* Meigen collected in June 1943 and June 1945 and from one pool of *Culex tarsalis* Coquillet collected in July 1944.

logical evidence of inapparent infection of man in Kern County, California, was easily found, but in only three cases of encephalitis did serological evidence of any type support or partially support supposition that the California virus caused the disease. Although numerous attempts have been made, virus of this type has not been isolated in a fatal human case nor from specimens of blood taken during the acute phase. Following are reports of the three cases in which there was indication that the disease might have been caused by the California virus.

CASE 1: The patient, a 2-month-old male of Mexican descent, had residence and potential exposure in Delano, California (Kern County). On September 6, 1945, the mother noticed that the child was very irritable and cried out periodically as if in severe pain. Occasionally he had convulsions. He had not vomited, but the mother said he had been constipated. The illness continued for two days before she took the child to the outpatient department of the Kern County General Hospital. He was immediately hospitalized (Sept. 8), with a diagnosis of encephalitis. The child was thin and acutely ill. The anterior fontanelle was bulging. He lay in hyperextension with eyes fixed and rotated upward. No abnormalities were noted in examination of the ears. The chest was clear. The abdomen was rigid, but the patient was crying hard. Tendon reflexes were hyperactive and muscles were tense. The rectal temperature upon admittance was 104 degrees F. The maximal rectal temperature (degrees Fahrenheit) on each of the six following days was: 104.6, 104.4, 104.0, 101.0, 100.4, 98.8; and from then on it was normal.

A spinal tap was made just after admittance to hospital and injections of penicillin were started, 5,000 units every three hours night and day until Sept. 13.

In the first two days in the hospital the child had convulsions several times a day when disturbed, and there were frequent twitchings. He remained very "rigid," slept a great deal and had to be fed by gavage. By Sept. 11 (fourth hospital day), definite clinical improvement was noted. By Sept. 13 he took his formula by bottle and retained it, and then appeared more relaxed. He was discharged from the hospital shortly thereafter.

(Later the health department tried to locate the child but was unsuccessful. Three years later a research staff nurse found the family. She was told by the mother that the child had not recovered completely from the illness and had continued to have occasional mild convulsions. He had never been able to sit up and constantly held his left arm "drawn up." He had died at home of what his mother stated was pneumonia, at the age of 11 months.)

Results of laboratory examinations in Case 1 were:

September 8. Spinal fluid: leukocytes 2,875 per cu. mm., all polymorphonuclear cells; appearance, cloudy; no organisms observed in a smear; globulin reaction, 3 plus.

September 10. Result of a Kahn test was negative for syphilis. There was a faint trace of albumin but no sugar in the urine, and occasional erythrocytes and a few bacteria were noted. Erythrocytes numbered 2,240,000 per cu. mm. of blood, and the hemoglobin content was 5.7 gm. per 100 cc. The color index was 84. Leukocytes numbered 10,400 per cu. mm.—56 per cent lymphocytes, 37 per cent polymorphonuclear cells, and 2 per cent monocytes. The spinal fluid contained 760 cells per cu. mm.—71 per cent lymphocytes and 29 per cent polymorphonuclear cells. It was slightly turbid. The globulin reaction was 3 plus. Sugar content was 41.6 mg. per 100 cc. No organisms grew on a culture and none were observed on a smear. The gold curve was 0000023211.

September 13. In an x-ray film of the chest the lung fields were observed to be clear. Result of a Mantoux test was negative for tuberculosis.

September 15. Erythrocytes numbered 2,320,000 per cu. mm. of blood and the hemoglobin content was 7.1 gm. per 100 cc. Leukocytes numbered 12,050—lymphocytes 40 per cent, basophils 2 per cent, eosinophils 2 per cent, myelocytes 4 per cent, stab cells 7 per cent, polymorphonuclear cells 42 per cent, and monocytes 3 per cent.

*Virus studies.* Blood serum withdrawn and frozen on September 8 (two days after onset of illness) was injected in mice and guinea pigs by the combined intracerebral and intraperitoneal route. Virus could not be isolated by this means. A specimen of the same serum was tested for neutralizing antibodies against western equine, St. Louis and California virus (strain BFS-283) simultaneously with a specimen drawn on September 20 (14 days after onset). A 1:10 serum dilution of acute and convalescent specimens protected all the mice against 5,000 $LD_{50}$* of western equine virus (antibodies probably of maternal origin). Antibody against St. Louis virus was not detectable at the level of a 1:10 serum dilution in either specimen. Both specimens were tested twice in a 1:10 dilution against approximately 25 and 250 $LD_{50}$ of the California virus. The first specimen offered no apparent protection against California virus in either test, but protection was complete against both dilutions of virus in both tests with the convalescent specimen. The results of the neutralization tests (no change in titer to western equine virus, absence of St. Louis virus antibody and a rising titer from negative to protection against more than 250 $LD_{50}$ of the California virus) support the diagnosis of California virus infection.

Complement-fixation tests were performed against the antigens of western equine, St. Louis and Russian spring-summer encephalitis viruses (the latter as a mouse brain control, since all antigens were prepared from mouse brain), but the reactions were slightly anticomplementary. However, the titers with each antigen (positive in a 1:2 or 1:4 dilution of serum only) were identical, indicating that there

*5,000 times the lethal dose for 50 per cent of mice.

were no complement-fixing antibodies against the western equine or St. Louis viruses and confirming a belief that the neutralizing antibodies for western equine virus were of a maternal source and probably not acquired during the current illness. Data from studies of mares and colts show that although maternal neutralizing antibodies against western equine virus are regularly transmitted to the offspring, complement-fixing antibodies are not. Unfortunately, at the time of the illness of the patient complement-fixing antigens had not been prepared from the California virus. The serological evidence of BFS-283 (California virus) infection in this case appears to be very strong.

Although the sugar content in the spinal fluid was slightly low and the cell content relatively high for a virus infection, neither excludes the possibility of a virus infection. In small infants infected with the equine viruses, cell content is occasionally as high as it was in the present case. In light of the fact that the hospital laboratory, at about the same time, reported slightly low spinal fluid sugar content in other cases of what was believed to be virus infection of the central nervous system, it is possible that a laboratory error occurred; or the fluid may have been held overnight before testing, a common practice in that hospital at the time.

CASE 2: A white boy 7 years of age who had lived in Arvin, California (Kern County) for three weeks, became ill Aug. 12, 1945. He was hospitalized Aug. 18 with a preliminary diagnosis of encephalitis or meningitis. The parents reported that fever had developed six days before admittance and that the maximal temperature was 104 degrees F. The patient had vomited, lost appetite, then had become drowsy and finally complained of headache. The maximal temperature during the hospital stay was 102.4 degrees F. When the patient entered the hospital, the spinal fluid contained 175 cells per cu. mm., all lymphocytes. There was a trace of globulin in the fluid, and the sugar content was 34.8 mg. per 100 cc. Leukocytes per cu. mm. of blood numbered 5,500—52 per cent lymphocytes. Paralysis was not present and the patient was discharged Aug. 24. The diagnosis was encephalitis, type unknown. When examined again Sept. 4 the patient had no apparent residual effects.

*Virus studies.* Specimens of blood were obtained six and 24 days after onset of illness. Neutralizing antibodies for western equine or St. Louis virus could not be demonstrated. When these specimens were tested for complement fixation a year later, both were anticomplementary. Serum (undiluted) drawn in the acute phase of the illness did not neutralize California virus (BFS-283) at a level of 25 and 125 $LD_{50}$, while in three separate tests the specimen taken during convalescence gave a neutralization index of approximately 125.* A 1:5 serum dilution of the convalescent specimen offered partial protection against both dilutions of virus. Unfortunately, the acute phase serum became contaminated and it could not be used to repeat the neutralization test against California virus to confirm the negative result in the first test. Thus, the serological evidence in this case is not quite as strong as that in Case 1, but it would ordinarily be considered confirmatory diagnostic evidence for a well-recognized type of virus disease.

CASE 3: A white agricultural worker 22 years of age, living in Arvin, California (Kern County) became ill on Aug. 30, 1945, and was hospitalized at Kern County General Hospital on Sept. 2 with a provisional diagnosis of encephalitis. The course of illness was that of typical mild encephalitis or non-paralytic poliomyelitis, with fever up to 102.2 degrees F., severe headache, and stiffness of the back and neck. The cerebrospinal fluid contained 28 cells per cu. mm., of which 52 per cent were polymorphonuclear. Reaction to a test for globulin was negative. No other tests were performed on the fluid. At the time of admittance, leukocytes numbered 10,300 per cu. mm. of blood. The patient recovered after an illness lasting approximately one week.

*Virus studies.* Blood specimens were obtained two and 13 days after onset of illness. Virus could not be isolated from the acute phase specimen. There were no neutralizing antibodies against the western equine virus in either serum. In a "screen test" against the St. Louis virus, the convalescent specimen protected three of four mice against 15 $LD_{50}$ of virus. In a repeat, quantitative test, including the acute phase serum, using undiluted serum against 25 and 250 $LD_{50}$ of virus, the convalescent specimen again protected slightly and the acute phase serum did not protect. The neutralization index of the convalescent specimen was calculated to be between 25 and 50, the equivocal range. At the same time the two specimens were tested in a 1:5 dilution against 25 and 250 $LD_{50}$ of St. Louis virus, and in this dilution neither specimen protected against either dosage of virus. This confirmed the result of the test on the undiluted serum, indicating that the antibody titer was not in the range of significance. When the complement-fixation test was made, the serum from the early specimen was anticomplementary and the convalescent specimen gave positive reaction in a dilution of 1:8 with the St. Louis virus in two separate tests, and negative reaction to western equine and Russian spring-summer viruses, the latter used as an antigen control for the mouse brain component. The results of both the neutralization and complement-fixation tests are what might be expected in the early phase of a St. Louis infection; the second specimen of serum was taken only 13 days after onset of the illness, and neutralizing antibodies to this virus usually develop quite slowly. However, the titers by both types of test lie in the equivocal range. Since the authors were not satisfied that a serological diagnosis had been made, both specimens (undiluted) were then tested for neutralizing antibody to California virus, using 20

*The neutralization index expresses the amount of protection afforded by the serum in terms of comparison with a normal serum specimen. In most encephalitis virus infections, any index of 50 or greater is considered significant.

and 100 $LD_{50}$ of virus. There was no protection by the acute phase serum, but almost complete protection against both virus dilutions was afforded by the convalescent specimen, giving it a neutralization index slightly greater than 100, which it is believed should be considered significant. Not enough serum remained for further testing of any kind.

It is difficult to say whether California or St. Louis virus was the etiological agent (in Case 3) or whether a combination of the two or independent infections with both, the one following the other after a short interval, was responsible. It has been well established that the two are unrelated immunologically.[9] However, there was slightly stronger evidence that California virus was the infective agent than that it was the St. Louis virus.

## ADDITIONAL VIRAL STUDIES

For several years the authors have made combined clinical and virus studies in cases of suspected neutropic virus infections in Kern County General Hospital. Specimens of sera and feces have been collected routinely. In the early years of the study these specimens were refrigerated; more recently they have been frozen and transported to the San Francisco Neurotropic Virus Unit at the Hooper Foundation under temperature conditions similar to those employed for storage. Efforts were made by means of neutralization and complement-fixation tests to aid in the specific etiologic diagnosis of western equine and St. Louis encephalitis and mumps meningoencephalitis. In cases in which there was no serologic evidence of these diseases and in which there was no flaccid paralysis, the feces were usually tested for poliomyelitis virus.

After isolation and adaptation of the three strains of California virus, sera from the large residual of undiagnosed cases were tested for antibodies against the California virus. Smaller numbers of sera from patients from other parts of California were also tested. This series of tests with the California virus began with the summer collection of 1944 and continued through 1949. It was in this series that the rising titers of neutralizing antibody were noted in the three cases reported herein. In the latter part of 1946 a benzene-extracted complement-fixing antigen for the California virus was prepared,[2] and a few sera were tested for both neutralizing and complement-fixing antibodies that year. In 1947, 1948 and 1949, the complement-fixing antigen was included with a "battery" of antigens (usually western equine, eastern equine, St. Louis, Japanese B, mumps, New Castle and California viruses) used for the primary testing of the sera from all patients. The California virus neutralization test was applied to these sera, when the result of every other test, including neutralization tests for western equine and St. Louis virus, was negative or the titer did not increase after the infection, provided there was an adequate amount of serum left. In many instances sufficient serum was not available.

1. *Neutralization Tests.*

*Method.* Infected mouse brains were triturated in a 10 per cent rabbit serum-broth to make a 10 per cent mouse brain suspension. This was slowly centrifuged and the supernatant frozen as a source of virus. Serial five-fold or ten-fold dilutions of virus were prepared in a 10 per cent rabbit serum-broth. After selecting appropriate virus dilutions, 0.2 ml. of each was mixed with 0.2 ml. of undiluted serum and the mixtures were then incubated for two hours at 37° C. All tubes were then placed in an ice-water bath. Mice were inoculated with the serum-virus mixtures, beginning immediately after the two-hour incubation period. Animals, three to four weeks old, were inoculated intracerebrally in groups of four. Deaths were recorded for a period of ten days. In the early tests, two dilutions of virus representing 10 to 20 and 50 to 100 $LD_{50}$ of virus were used. In later years, four or five ten-fold dilutions of virus were employed. The highest dilution was the equivalent of 25 to 50 $LD_{50}$ and the lowest 1,000 to 10,000 times this amount of virus. Any serum that neutralized 10 to 20 $LD_{50}$ was classified as equivocal and any that neutralized 50 to 100 $LD_{50}$ as positive.

2. *Complement-fixation* tests were performed with the modified benzene-extracted antigen described by Espana and Hammon[2] and the control sera made in guinea pigs by the method of Hammon and Espana.[5] The technique employed in the test was essentially that described by Casals.[1]

## RESULTS

Sera from 188 patients were tested for neutralizing antibody against California virus. The results were positive in 11.1 per cent of the cases, equivocal in 7 per cent, negative in 81.1 per cent. Two hundred and ninety-four pairs of sera were subjected to the complement-fixation test and the results in all cases were completely negative. The neutralization test results are presented in Table 1. None of the sera can be assumed to be from cases of current infection with this virus, because either they were negative or the titer of the convalescent phase specimens was no higher than that of the acute phase serum. The results are interpreted to represent the effect of previous experience with the virus and probably are fairly representative of the infection rates in the general population of this area. In Table 1, in calculating the percentage of positive reactions, the equivocal results were calculated both as positive and negative, since it is uncertain in which group they properly belong. The cases are tabulated by

TABLE 1.—*Results of neutralization tests on sera of persons* residing in Kern County, California, by age and by years of residence in the county.*

| Results | Residence in county in years | | | | | Age in years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1-4 | 5-9 | 9 | Unknown | <1 | 1-4 | 5-9 | 10-14 | 15-19 | 20-29 | >29 | Unknown | Total |
| Negative | 25 | 62 | 32 | 21 | 14 | 11 | 30 | 38 | 25 | 15 | 18 | 14 | 3 | 154 |
| Equivocal† | 1 | 4 | 6 | 1 | 1 | 0 | 2 | 1 | 3 | 3 | 0 | 2 | 2 | 13 |
| Positive | 4 | 5 | 2 | 5 | 5 | 0 | 0 | 2 | 1 | 3 | 8 | 7 | 0 | 21 |
| Total | 30 | 71 | 40 | 27 | 20 | 11 | 32 | 41 | 29 | 21 | 26 | 23 | 5 | 188 |
| % Positive‡ | 13.3 | 7.0 | 5.0 | 18.5 | 25.0 | 0 | 0 | 4.9 | 3.4 | 14.3 | 30.8 | 30.4 | 0 | 11.1 |
| % Positive and equivocal | 16.7 | 12.7 | 20.0 | 21.4 | 30.0 | 0 | 6.2 | 7.3 | 13.8 | 28.6 | 30.8 | 39.1 | 40.0 | 18.1 |

*These results were obtained with the convalescent phase serum of patients apparently suffering from a neurotropic virus infection, but in no instance in this group was the second titer higher than the first when the second was positive.

‡All equivocal results considered negative.

†Serum neutralizing 10 to 20 $LD_{50}$ was classified as equivocal.

length of residence of the patient in the county and by the age of the patient. The length of residence could not be determined for 20 persons; tests of sera from five of them were positive for the virus, and from one equivocal. Proper distribution of these might significantly change the results in any one group. Although positive reactions occurred in an unexpectedly large number of cases after only one year of residence, there appeared to be a trend toward increasing incidence of positive reaction as the length of residence in the area increased. The proportion of infected persons increased with age. If the virus neutralization indicates previous infection, it is quite obvious that infection rates are high in the community. Since results of tests failed, except in rare instances, to identify this agent as the cause of clinical disease of the central nervous system, if infection frequently produces clinical disease, it is generally a form of disease not yet suspected and, therefore, not studied for a serological response to this virus. On the other hand it seems more likely that infection is inapparent in most instances. The immunity rates observed are closely comparable to those observed in surveys in the same community made in a similar manner for western equine infection, but considerably lower than for the St. Louis virus.[11] The age distribution of the inapparent infections produced by the latter two viruses,[11] however, does not parallel that of the California virus, suggesting that the principal vectors and conditions of exposure are not identical. In further support of this hypothesis is the fact that in two of the three instances in which the California virus was isolated it was from *Aedes dorsalis*[9], and isolations of western equine and St. Louis viruses have rarely been obtained from this species, but are usually from *Culex tarsalis*.[4] Further support is gained from the differences in distribution of antibodies found in rodents and birds, to be discussed later in this paper.

In 1948 this virus was supplied to Dr. John B. Enright, then at the Viral and Rickettsial Disease Laboratory of the California State Department of Public Health, who tested paired sera in cases of suspected neurotropic virus infections, including poliomyelitis, from all portions of California, except Kern County. Dr. Enright and Dr. E. H. Lennette, director of the laboratory, reported to the authors the results of these tests on sera from 1947 and 1948. The total number of cases from California in the survey, identified by geographical area, was 292. There were 23 instances of positive reaction, and in only one instance did the titer rise between an early and a late serum, and in that case the rise was not considered significant. Most of the patients who had positive reaction (14) were from the central valleys (Sacramento and San Joaquin), two from the San Bernardino Valley, two from Los Angeles and five from the San Francisco Bay area. Of 157 patients from the hot valley areas where other mosquito-borne diseases occur, 10 per cent had positive reaction, while 5.2 per cent of 135 from all other areas had positive reaction. These differences are not statistically significant, but are in the direction expected. It is interesting to note that the percentage of positive results in patients from the three hot valley areas was almost identical to that in Kern County (11.1 per cent). The infection rate for California as a whole was 23 of 292 (7.9 per cent).

Specimens of blood from persons who lived outside of California were tested in an attempt to obtain some information regarding the geographical distribution of the virus and indirectly to obtain information about the specificity of the neutralization test in man. The results are presented in Table 2. Specimens from ten adults in the state of Washington, five in Colorado and 24 in Tokyo were all negative for the disease. Among the specimens from Colorado and Japan not a single equivocal result was obtained. This evidence supports the specificity of the results in Kern County and suggests that the "equivocal" results in Kern County were also significant. It also suggests that geographic distribution of the virus may be somewhat limited.

Further evidence of the limited distribution of the virus and the specificity of the neutralization test has been obtained from other investigators to whom supplies of the strain BFS-283 of the California virus were sent. Dr. Herbert A. Wenner of the University of Kansas reported that in tests of specimens from

**TABLE 2.—*Results of neutralization tests for California virus infection in man and other animals from areas outside of the San Joaquin Valley.***

| Animal and Area | Positive | Negative | Total |
|---|---|---|---|
| Man (Valley City, N.D.) | 0 | 7 | 7 |
| Man (Yakima Valley, Wash.) | 0 | 10 | 10 |
| Man (Colorado) | 0 | 17 | 17 |
| Man (Tokyo, Japan) | 0 | 24 | 24 |
| Man (Garden City, Kan.) | 0 | 6 | 6 |
| Ground squirrel (Northern Calif.) | 0 | 6 | 6 |
| Calf (Northern Calif.) | 0 | 2 | 2 |
| Jack rabbit (Yakima Valley, Wash.) | 0 | 23 | 23 |
| Cottontail rabbit (Yakima Valley, Wash.) | 0 | 2 | 2 |
| Total | 0 | 97 | 97 |

seven patients in Valley City, North Dakota, and from six who lived in Garden City, Kansas, all with disease of unidentified cause, there were no positive results. He stated that in all cases the neutralization index was below 10. Dr. Morris Schaeffer of the U.S.P.H.S. Communicable Disease Center Laboratories reported that he had had specimens from twelve patients in Colorado tested, using 17 and 170 $LD_{50}$ of virus. Results were negative.

#### CLINICAL DISEASE IN ANIMALS OTHER THAN MAN

In the laboratory, no recognized disease has occurred regularly in any species of animal experimentally infected with the virus by a subcutaneous or intraperitoneal route, or fed on by an infected mosquito. Clinical disease has been produced consistently only by intracerebral inoculation, a highly artificial route.

In the field, animal disease known to be due to this virus has not been encountered. Eight horses in Kern County that had encephalomyelitis were studied serologically to determine if the California virus were the responsible pathogenic agent. T. K. Brunner, D.V.M., of the Hooper Foundation, obtained specimens of blood during the early acute stage, if possible, or as soon thereafter as the disease was reported, and again later, usually after recovery. The specimens were examined first by neutralization test against the western equine and St. Louis viruses, and when none could be identified satisfactorily by this procedure, they were tested for complement-fixing antibodies against California, western equine and St. Louis antigens. In five of the eight cases results were negative by all the types of tests used and with all viruses.

The late serum specimen from one horse gave positive reaction in a dilution of 1:8 in the complement-fixation test with the California virus. The amount of serum from the earlier specimen was inadequate for performance of a similar test on it. However, the neutralization index for western equine virus increased from 248 to 14,500 in specimens collected 34 and 43 days, respectively, after onset. However, as the antibody response to western equine infection in horses is known to occur extremely early in the course of the disease, it is probable that the western equine infection occurred after the clinical disease and was not the cause. The disease, therefore, might have been caused by California virus.

Three specimens obtained from another horse, 2, 16 and 33 days after onset, all had a very high titer by neutralization test and by complement-fixation test to the western equine virus. For St. Louis virus the complement-fixation titer of the second day specimen was 1:8; of the 16th day specimen less than 1:4, and of the 33rd day specimen 1:16. For California virus the two earlier specimens gave negative reaction while the 33rd day specimen was positive in a 1:8 dilution. These results, although too confusing for definite interpretation, suggest that the California virus might have played a role.

Thus, in the cases of two horses serologic evidence was suggestive, although far from conclusive, that clinical disease was caused by the California virus.

#### INAPPARENT INFECTION OF ANIMALS OTHER THAN MAN

Soon after the California virus was isolated, attempt was made to find out what animals are infected under natural conditions in Kern County. Table 3 presents the results of a small-scale survey with the neutralization test. Immunity rates were relatively high in almost all mammals tested. The few large mammals tested were heavily involved, as they are with St. Louis and western equine infections. But a fairly high proportion of rabbits and ground squirrels also had positive serologic response, whereas not many of these small animals had positive reaction in earlier studies with the other two viruses.[6] These observations in the field led to tests in the laboratory to determine whether ground squirrels and rabbits might be a source of infection for mosquitoes. Results of those tests, as reported in another paper in this series,[9] were suggestive.

In eleven chickens tested there was no California virus antibody (Table 3) and, in the laboratory, inoculated chickens did not develop protective substances.[9] These results differ from those previously obtained in studies of chickens for reaction to the other two encephalitis viruses of the same area.[6]

To compare indirectly the significance of some of these results and at the same time to seek information regarding the geographical distribution of the virus, specimens of blood were obtained in other areas from some of the same species of animals that in Kern County had positive reaction in serologic tests. Results are presented in Table 2. Results of tests on ground squirrels and calves from North-

TABLE 3.—*California virus-neutralizing antibodies in Kern County wild and domestic animals*

| Common name | Positive | Equivocal | Negative | Total tested |
|---|---|---|---|---|
| Cottontail rabbit | 3 | 4 | 14 | 21 |
| Jack rabbit | 4 | 1 | 17 | 22 |
| Ground squirrel | 11 | 20 | 26 | 57 |
| Antelope squirrel | 0 | 0 | 1 | 1 |
| Horse | 8 | 0 | 0 | 8 |
| Cow | 3 | 0 | 0 | 3 |
| Chicken | 0 | 3 | 8 | 11 |
| Total | 29 | 28 | 66 | 123 |

ern California and on rabbits from Yakima Valley, Washington, were negative. Apparently antibody encountered in rabbits in Kern County may be specific and infection absent or less frequent in these other areas.

In 1947 a serologic survey of normal horses was made in the San Joaquin Valley, California, with the help of Dr. Brunner. Specimens were obtained from horses of various ages in July and again from the same horses in September to determine the proportion in which inapparent infection with the St. Louis and western equine viruses developed. Some of the specimens were also tested for complement-fixing antibody against the California virus. Blood from 34 of the animals did not fix complement at any time. A specimen from one horse, 12 months of age, that was drawn July 8 gave a negative reaction, while a second specimen drawn September 11 had a titer of 1:8.

The only conclusions that could be drawn from these equine studies were (1) complement-fixing antibodies to the California virus occasionally develop during the summer season, and (2) complement-fixing antibodies must be temporary, as are those for other arthropod-borne encephalitis viruses, since on the basis of previous sampling with the neutralization test a high proportion (all of eight tested had positive reaction) had been infected previously.


## ACKNOWLEDGMENT

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# Carcinoma of the Colon

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*• In a study of statistical data on 1,215 patients with carcinoma of the colon observed at a university hospital in a twenty-year period, it was noted that the overwhelming majority of patients who were living five years after operation had had no demonstrable extension to lymph nodes at the time of operation. In an increasing proportion of cases in the latter years of the period, diagnosis was made before the lesion was beyond an operable stage.*

*What with today's better surgical techniques that make it possible to adapt operation to a variety of situations that may be encountered when the diseased area is visualized, and with better methods of preparing a patient and of sustaining him during operation, the wide excision so often necessary for cure may now be carried out deliberately and without hurry.*

*The site of the lesion has great bearing on the prognosis, owing to the limits upon the extent of operation in some locations as against the possibility of wide excision of the original lesion and areas of metastasis in others.*

AN OUTSTANDING achievement of the past quarter century has been the decrease in morbidity and mortality associated with operations for cancer of the colon. The rather formidable operations of 25 years ago have become almost commonplace procedures. The gains are attributable to the introduction and perfection of basic surgical techniques for operations on the large bowel and to application of more efficient methods for diagnosis of cancer at an early stage. More meticulous preparation of the large bowel with intestinal antiseptics, the use of parenteral antibiotics and the adequate replacement of whole blood during operative procedures are measures which permit unhurried and deliberate operation. An ever broadening experience in surgical techniques permits wider excision of actually or potentially involved malignant tissue, with the prospect of offering a curative procedure to an increasing number of patients.

During the 21-year period from July 1930 to July 1951, 1,215 patients with carcinoma of the colon and rectum were observed at the University of California Hospital. Adequate five-year follow-up data are available on 852 of them (Table 1).

It was not possible to offer a curative operation to all of the 1,215 patients observed during the period of study. The malignant lesions were resectable in but 786 patients (64.7 per cent) while the remaining 429 patients had a palliative procedure, exploratory laparotomy, or purely supportive therapy (Table 2). It is apparent that the number of patients having resections has been increasing in later years, since in the group treated before 1946 the resectability rate was 59 per cent.

Definitive resection was performed in 503 patients five years or more before July 1951 with a five-year survival rate of 47.9 per cent (Table 3). It is significant that relatively few of the patients who had lymph node metastases at the time of operation were living at the end of five years and that the overwhelming majority (80 per cent) of patients who were living after a five-year period were those who had no demonstrable lymph node metastases at the time of operation.

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**TABLE 1.—Carcinoma of the Colon and Rectum (University of California Hospital, 1930 to 1951)**

| Site of Lesion | Number of Cases | Treated 5+ Years Ago | Survived 5+ Years | Per Cent Survived 5+ Years |
|---|---|---|---|---|
| Colon | 549 | 370 | 119 | 32.2 |
| Rectum | 666 | 482 | 122 | 25.3 |
| Total | 1,215 | 852 | 241 | 28.2 |

**TABLE 2.—Increasing Proportion of Cases in Which Lesion Was Resectable at Time of Diagnosis**

| | Total Series 1930-1951 | | Treated 5 Years Prior to 1951 | |
|---|---|---|---|---|
| Site of Lesion | Number Patients | Resectability Per Cent | Number Patients | Resectability Per Cent |
| Colon | 549 | 65.2 | 370 | 60.8 |
| Rectum | 666 | 64.1 | 482 | 57.6 |
| Total | 1,215 | 64.7 | 852 | 59.0 |

**TABLE 3.—Comparative Results in Cases in Which Metastasis Was and Was Not Present at Time of Operation**

| | Metastases at Operation | No Metastases at Operation | Total |
|---|---|---|---|
| Operations | 191 | 312 | 503 |
| Living five years | 47 | 194 | 241 |
| Per cent five-year survival | 20 | 80 | 47.9 |
| Deaths within five years | 143 | 119 | 262 |
| Per cent mortality | 55 | 45 | 52.1 |

**TABLE 4.—Procedures Used for Right Colectomy**

| Operative Procedure | Number Patients | Living and Well 5 Years or More | Living with Recurrence | Per Cent Living, Well |
|---|---|---|---|---|
| One-stage resection | 53 | 32 | 0 | 60.4 |
| Two-stage resection | 12 | 5 | 2 | 41.7 |
| Mikulicz resection | 2 | 0 | 0 | 0 |
| Total | 67 | 37 | 2 | 55.2 |

**TABLE 5.—Survival After Right Colectomy in Cases in Which Metastasis Was and Was Not Present**

| | Metastases at Operation | No Metastases at Operation | Total |
|---|---|---|---|
| Operations | 29 | 38 | 67 |
| Living five years | 11 | 28 | 39 |
| Per cent five-year survival | 28.2 | 71.8 | 58.2 |
| Deaths within five years | 18 | 10 | 28 |
| Per cent mortality | 64.3 | 35.7 | 41.8 |

**TABLE 6.—Survival After Transverse Colectomy in Cases in Which Metastasis Was and Was Not Present**

| | Metastases at Operation | No Metastases at Operation | Total |
|---|---|---|---|
| Operations | 5 | 8 | 13 |
| Living five years | 2 | 5 | 7 |
| Per cent five-year survival | 28.6 | 71.4 | 53.8 |
| Deaths within five years | 3 | 3 | 6 |
| Per cent mortality | 50 | 50 | 46.1 |

**TABLE 7.—Procedures Used for Transverse Colectomy**

| Operative Procedure | Number Patients | Living and Well 5 Years or More | Living with Recurrence | Per Cent Living, Well |
|---|---|---|---|---|
| One-stage resection | 5 | 4 | 1 | 80 |
| Two-stage resection | 6 | 1 | 0 | 16.6 |
| Mikulicz resection | 2 | 1 | 0 | 50 |
| Total | 13 | 6 | 1 | 46.1 |

Right colostomy was performed on 67 patients five years or more before July 1951. In the majority of patients the operation was done in one stage (Table 4). The two-stage resection and the Mikulicz procedure were performed in a relatively small number of cases. Of those patients who underwent definitive right colectomy, 58.2 per cent were alive at the end of five years (Table 5) and the survival rate was considerably higher in the group of cases in which there was no metastasis at the time of operation.

It is generally agreed that cancer of the large bowel which can be extirpated should be dealt with radically not only by wide excision of the primary growth and the adjacent bowel but also by radical removal of the contiguous gland-bearing tissue. The favorable prognosis associated with lesions on the right side of the colon appears to bear direct relationship to the ability to remove wide expanses of mesentery by virtue of the anatomy in this area.

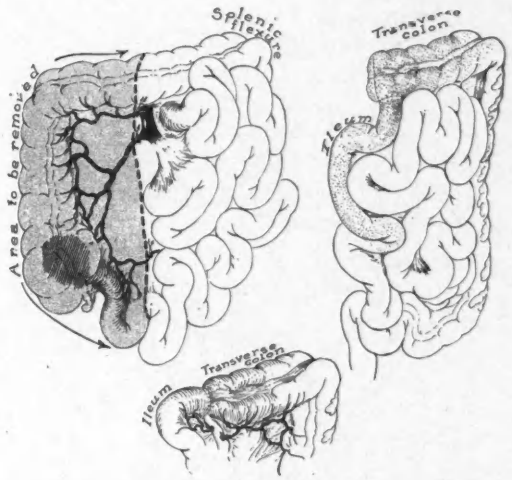


**Figure 1.—Wide expanse of lymph node-bearing mesentery removed in the resection of right colon lesions. End-to-end anastomosis can usually be accomplished although when the disparity in diameter of the two segments is considerable an end-to-side ileotransverse colostomy must be used.**

In the one-stage right colon resection, for example, the usual procedure is removal of the entire mesentery of the right colon as well as a portion of the terminal ileum and its mesentery. The ease with which intestinal continuity can be reestablished by ileotransverse colostomy after removal of a large amount of gland-bearing mesentery has made such a procedure almost a standard one (Figure 1). The less favorable outlook for malignant lesions lower in the large intestine (the lower the lesion the poorer the prognosis) is owing at least in part to the inability to remove such wide areas of actually or potentially involved tissue.

Of 13 patients who underwent transverse colectomy,* eight were without lymph node metastases while five had evidence of metastatic deposits at the time of operation. Seven of the 13 patients were alive at the end of five years, and five of the seven patients who had no metastases at the time of operation (Table 6). As is true with regard to other segments of the large intestine, the presence of regional lymph node metastases even in those areas which are amenable to wide mesenteric excision makes for a much poorer outlook (Figure 2).

In this series the number of two-stage procedures in the treatment of lesions of the transverse colon was greater than the number of primary one-stage transverse colectomies (Table 7). The fact that so few of the patients survived the staged resections indicates not a failure of the procedures themselves

* Fifteen patients with lesions of the transverse colon had right colectomy; thirteen patients with lesions there had left colectomy. The cases are included in the statistics of the right and left colectomy groups respectively.

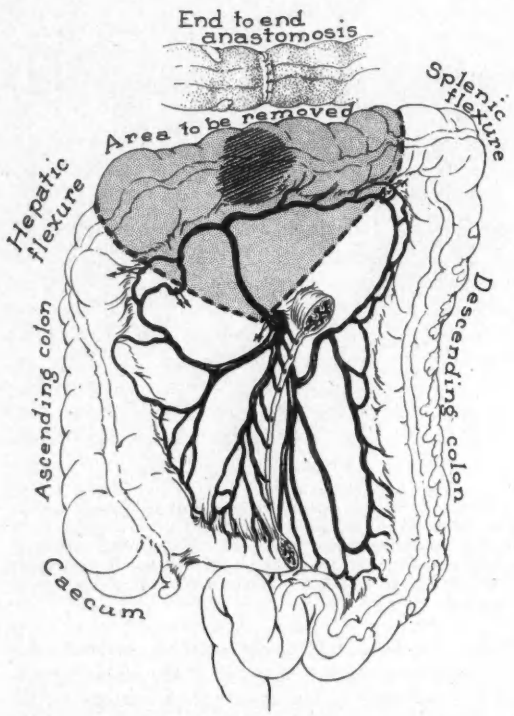


Figure 2.—The ability to mobilize the hepatic and splenic flexures of the colon permits end-to-end anastomosis after wide excision of growths in the transverse colon.

but rather the advanced state the lesion had reached before operation was done.

It must be acknowledged that although a one-stage primary resection of cancer of the large intestine is the surgical procedure of choice and, where applicable, provides the better prognosis because of the more favorable state of the lesion, in many patients staged procedures are mandatory. This is especially true in the presence of chronic obstruction of the large bowel with its accompanying debilitation, dehydration and generally lowered physiologic state. In the presence of such a multiplicity of variable factors, the ability to adapt a program of surgical treatment to the problem at hand is perhaps the greatest of assets, for that ability will be reflected in morbidity, mortality and prognosis.

There were 145 patients who had resections for lesions of the left colon. The five-year survival rate was considerably higher for patients who did not have metastatic deposits at the time of operation (Table 8).

Various methods of treatment were applied to lesions in the left colon, including the Mikulicz resection, anterior resection, one-stage segmental resection with or without concomitant cecostomy or proximal colostomy, two-stage segmental resection with proximal decompression, abdominoperineal resection and, in one instance, a local excision. The modern concept of definitive resection of lesions of the left colon by so-called segmental excision, either with or without concomitant decompression of the proximal colon by means of cecostomy or transverse colostomy, appears to be justified by favorable results. In the present series the highest survival rate was associated with that procedure (Table 9). However, it must be remembered that other surgical procedures have a definite place in the treatment of selected patients. In general, these procedures were used when the condition of the patient was thought to be sufficiently precarious to indicate the use of an operation of lesser magnitude than primary resection. At the same time, the earlier diagnosis of cancer before obstructive symptoms develop, and the adequate preparation of the large bowel by intestinal antiseptics, have permitted the use of radical wide resection in one stage of malignant lesions of the colon not only with greater frequency but also with greater security.

Carcinoma of the rectum was treated with definitive operation in a group of 278 patients (Table 10). and here again the survival rate was much higher

**TABLE 8.—*Survival After Left Colectomy in Cases in Which Metastasis Was and Was Not Present***

| | Metastases at Operation | No Metastases at Operation | Total |
|---|---|---|---|
| Operations | 57 | 88 | 145 |
| Living five years | 14 | 59 | 73 |
| Per cent five-year survival | 19.2 | 80.8 | 50.4 |
| Deaths within five years | 43 | 29 | 72 |
| Per cent mortality | 60 | 40 | 49.6 |

**TABLE 9.—*Procedures Used for Left Colectomy***

| Operative Procedure | Number Patients | Living and Well 5 Years or More | Living with Recurrence | Per Cent Living, Well |
|---|---|---|---|---|
| Segmental resection with or without proximal colostomy | 98 | 48 | 3 | 49.0 |
| Mikulicz resection | 24 | 11 | 1 | 45.8 |
| Anterior resection | 16 | 7 | 0 | 43.8 |
| Abdominoperineal resection | 6 | 2 | 0 | 33.3 |
| Local excision | 1 | 1 | | 100.0 |
| Total | 145 | 69 | 4 | 47.6 |

**TABLE 10.—*Survival in Carcinoma of Rectum in Cases in Which Metastasis Was and Was Not Present***

| | Metastases at Operation | No Metastases at Operation | Total |
|---|---|---|---|
| Operations | 100 | 178 | 278 |
| Living five years | 20 | 102 | 122 |
| Per cent five-year survival | 16.5 | 83.6 | 43.9 |
| Deaths within five years | 79 | 77 | 156 |
| Per cent mortality | 50.6 | 49.4 | 56.1 |

**TABLE 11.—*Procedures Used for Carcinoma of the Rectum***

| Operative Procedure | Number Patients | Living and Well 5 Years or More | Living with Recurrence | Per Cent Living, Well |
|---|---|---|---|---|
| Perineal resection Preliminary colostomy (Lockhart-Mummery) | 95 | 40 | 1 | 42.1 |
| One-stage abdominoperineal | 131 | 45 | 6 | 34.3 |
| Anterior resection (Hartman) | 19 | 8 | 1 | 42.1 |
| Resection with anastomosis | 16 | 9 | 0 | 56.3 |
| Local excision | 17 | 11 | 1 | 64.7 |
| Total | 278 | 113 | 9 | 40.6 |

**TABLE 12.—*Operative Mortality in Cases in Which Definitive Therapy Was Carried Out***

| Site of Lesion | Number Patients | Number Deaths | Mortality Per Cent |
|---|---|---|---|
| Right colon | 106 | 8 | 7.4 |
| Transverse colon | 22 | 0 | 0 |
| Left colon | 230 | 15 | 6.5 |
| Rectum | 428 | 29 | 6.7 |
| Total | 786 | 52 | 6.6 |

for patients who were operated upon before metastatic extension of the lesion to lymph nodes.

In recent years, as mortality rates associated with operations on the rectum have diminished, the use of two-stage resection by colostomy and perineal excision has generally been abandoned at the University of California Hospital in favor of one-stage radical abdominoperineal resection (Table 11). The greatest number of perineal resections (Lockhart-Mummery) in the present series were performed in the earlier years of the study. Such procedures are usually reserved for dealing with low-lying lesions in elderly patients whose general physiologic state prevents the more radical one-stage operation. The fact that the survival rates associated with all the acceptable surgical procedures are comparable would indicate that the operations of lesser magnitude than the one-stage procedure should not be forgotten and should be applied where the general physical condition of the patient suggests the use of such specific surgical measures. In light of the reported results (Table 11) it is difficult to believe that combined abdominoperineal resection of the rectum, although generally accredited as the procedure of choice, will ever completely displace all other procedures in the surgical treatment of rectal cancer.

The highly favorable survival rate associated with local excision of rectal lesions can be explained by the pathologic nature of the lesions. Generally they were small polypoid tumors either with only histologic evidence of malignancy or with limited early

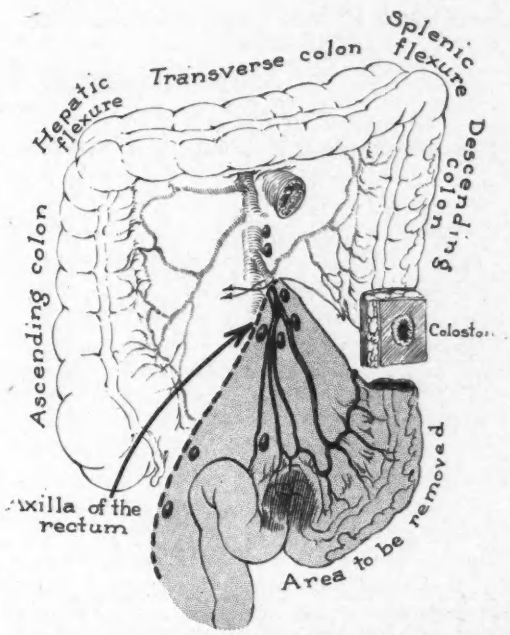


**Figure 3.—The removal of the lymph node-bearing area at the root of the inferior mesenteric vessels is essential. This area has been aptly termed "the axilla of the rectum." Nodes in the periaortic chain can also be excised. The generous en bloc removal of tissue accomplished by an abdominoperineal resection is evident.**

invasion of the base of the lesion. It is well known that limited procedures in such circumstances may very well produce favorable results.

The use of sphincter-preserving operations, including low-lying anastomosis following resection for carcinoma at or below the rectosigmoid junction, should be condemned. The incidence of local recurrences following such procedures is considerable. Abdominoperineal resection of the rectum for malignant disease of this area is the operation of choice. The wide resection of lymph node-bearing areas obtained by the one-stage radical combined operation is approached by none of the other recognized procedures for rectal cancer. Removal of wide expanses of the sigmoid mesentery and the lymph node-bearing area near the origin of the inferior mesenteric vessels and upward along the aorta is an absolute essential in the correct performance of the procedure. The area at the apex of the sigmoid mesentery at the root of the inferior mesenteric vessels has aptly been called the "axilla of the rectum" (Figure 3). The phrase denotes the necessity of meticulous en bloc dissection of the area similar to that universally accepted as standard procedure in the surgical treatment of carcinoma of the breast.

There is good evidence that the route of lymphatic metastasis from rectal carcinoma is almost entirely

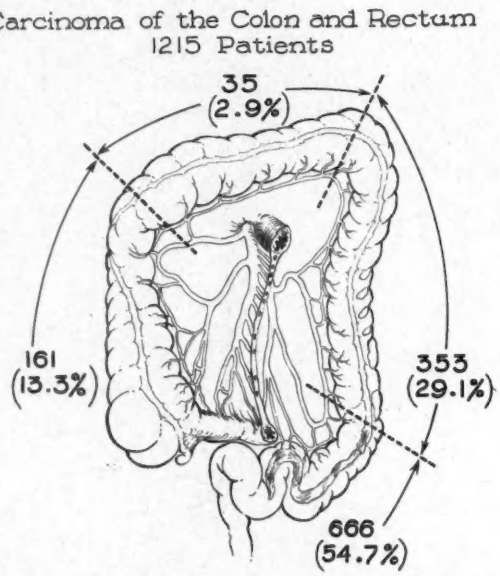


**Figure 4.—Malignant lesions arise in the left colon in a high proportion of cases. The great majority of these tumors were located in the sigmoid, rectosigmoid and rectal segments.**

upward. Downward spread occurs only when the lesion is far advanced and the upward channels are blocked by malignant cells. The adage that "cancer is a disease that is never treated too early and seldom too radically" applies most certainly in malignant disease of the rectum wherein the most radical procedure is obviously the operation of choice.

Data on operative mortality in the present series (Table 12) indicate that in excision of carcinoma of the large bowel the surgical risk is not much affected by the site of the lesion. The favorable data with regard to lesions of the transverse colon probably reflect the ease with which such lesions can be removed. The extent of the surgical procedure in these instances is generally less than is required for removal of lesions from other portions of the colon.

The incidence of malignant lesions in each of the various segments of the colon in the entire series of 1,215 cases is shown in Figure 4. In 83.8 per cent of the cases the lesions originated in the left colon and rectum. This accords, in general, with corresponding data on other series. The majority of lesions of the left colon were located in the sigmoid segment. The proportion of cases in which resection was possible was about the same regardless of the segment in which the lesion originated (Figure 5).

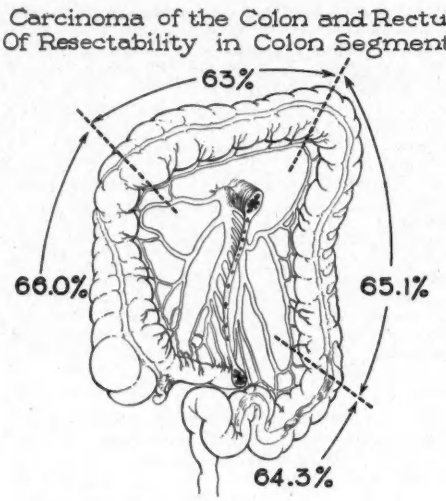


**Figure 5**

A significant fact not brought out in the tables presented is that none of the patients who had purely palliative or supportive treatment (429 patients during the 21-year period) survived five years. The authors believe, however, that in most instances palliative procedures are indicated since they usually provide some measure of comfort to the patient. Even in the presence of hepatic metastases, primary growths should be excised whenever possible, for in many instances the patient benefits.

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# Adventures in the Study of Breathing

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• *Perfect coordination is required between the amount of air breathed to ventilate the air cells of the lungs and the amount of blood pumped through them by the heart.*

*Over-ventilation often accompanies severe emotional disturbances with far-reaching effects on the functions of the brain and other organs. Of particular interest are the effects of altering breathing upon angina pectoris.*

*In conditions with under-ventilation the effects are serious because the carbon dioxide which accumulates acts as a narcotic on the nerve centers which control breathing. If oxygen is given to such patients they may be made much worse and become unconscious. Morphine and other narcotics also make matters worse.*

*Under-ventilation in patients with over-distention of the air cells of the lungs results in a chronic form of carbon dioxide poisoning, so that the lungs may fail in ventilatory function. Recent work by Whittenberger has shown how to combat this situation by mechanical over-ventilation. As the excess of carbonic acid is removed the narcotic effect of the gas is lessened and the nerve center governing breathing resumes more normal operation under which the effect of oxygen is no longer deleterious.*

THE RESPIRATORY FUNCTION taken as a whole involves the blood and its circulation as much as it does the ventilation of the lungs with air. The first two aspects of respiration have received full attention from clinical physiologists, but clinical observation of breathing has received far less than it deserves.

Certain abnormalities of breathing have been matters of commonplace observation for many decades. Thus we are all familiar with the orthopnea of congestive failure and of asthma; with the air hunger of Kussmaul, and the periodic breathing of Cheyne-Stokes. Less well known is the totally irregular breathing of Biot so commonly seen in tuberculous meningitis. How rarely, on the other hand, does one remark upon the exaggerated breathing in states of anxiety, unless it be of such degree as to precipitate tetany. Yet when one considers the vast number of unstable, anxious, insecure people, one realizes that we must be missing the basic mechanism underlying many bizarre symptoms of which they complain.

Many functions in the body are profoundly influenced by any change in the normal alkalinity of the blood plasma and the shifts in electrolyte equilibrium that accompany these changes. The most delicate and immediate adjustments of the reaction of blood plasma are met by the precise control of the rate and depth of breathing. If the volume of air breathed is abnormally augmented in relation to the demands of the metabolism of the moment, a loss of carbon dioxide will occur and immediately the blood reaction will become more alkaline. If the breathing volume is diminished relative to metabolic demand, carbon dioxide will accumulate and the blood will become less alkaline. In both instances the shift in blood reaction is ultimately compensated by shifts of electrolytes from cells to blood and vice versa, and by retention or excretion of base by the kidneys, and by appropriate alterations in blood flow. No doubt minor changes and compensatory adjustments are taking place all the time without production of symptoms. It is also probable that our failure to observe larger alterations in breathing deprives us of the clue to many symptoms accompanying neurotic or psychotic behavior, as well as many other obscure disorders of somatic and visceral functions.

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Guest speaker's address, presented before the Section on General Medicine at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

Let us take a common symptom such as the "night cramp" of the legs which wakens from sound sleep. Many remedies for this have been proposed, such as the use of venous stasis by light tourniquets or elevating the head of the bed slightly, or swinging the leg in dependency, or the use of quinine and other drugs. It may surprise you to learn that the simple procedure of holding the breath is frequently successful in relieving a night cramp. If you doubt this, try holding your breath the next time you experience one while sleeping in a Pullman upper berth and other measures for relief are not available.

I would like to direct your attention to another type of cramp, which is felt beneath the sternum during effort and which disappears on cessation of effort. I refer to that cramp called *angina pectoris*, which is intermittent and of short duration and not associated with electrocardiographic abnormality with the subject at rest. My attention was drawn to

an article by Friedell (in the August 1948 number of *Minnesota Medicine*) who discovered that the pain of angina pectoris was relieved by temporary arrest of breathing such as occurs when one listens intently. In investigating this phenomenon he found that he could teach patients with angina to avoid it by learning to breathe slowly, by voluntary restraint of breathing until this became automatic with them. I have been able to verify Friedell's observations. One patient walking briskly on a cold evening after dinner experienced the pain beneath the sternum. Instead of stopping to rest he simply held his breath for 15 or 20 seconds and the pain under the sternum ceased. Another patient, with mild angina of effort, whose electrocardiogram was normal at rest but became abnormal while walking on a treadmill, could also inhibit the pain by breath-holding. Another patient felt the pain during voluntary exaggeration of the breathing, yet did not feel it when hyperventilated by breathing carbon dioxide. This raised question as to whether angina pectoris could be a manifestation of over-breathing with ensuing hypocapnia and alkalosis.

Let us see how many of the known facts about angina will fit into such a hypothesis. First, it commonly occurs under circumstances of emotional excitement or stress in which over-breathing may occur. Second, its tendency to occur after meals suggests that the "alkaline tide" which occurs during secretion of hydrochloric acid in the stomach would enhance the alkalosis attendant upon over-breathing and loss of carbon dioxide. Third, we have the fact that an injection of epinephrine may induce angina. Of course, the direct effect of epinephrine on the coronary arteries is one of dilatation; but as this drug also produces pronounced stimulation of the breathing so as to bring on alkalosis and tetany at times, one may suppose that the effect on the breathing may be the predominant effect.

Let us examine some of the known facts about the effect of carbon dioxide upon the flow of blood through various organs. Kety and Schmidt[9] have shown that hyperventilation decreases the cerebral flow of blood. DeLalla found that hyperventilation diminished the volume of flow in the finger, as determined with an oncometer. By analogy, might it be that hypocapnia could bring about a diminution in flow of coronary blood by vasoconstriction?

Certain other phenomena of angina pectoris are worthy of consideration in this connection. In patients with aortic insufficiency, angina may occur while the heart is still compensated, but the pain may be entirely lacking when decompensation has occurred. If oxygen lack were the determining factor, one would expect the angina to be worse during congestive failure. Can it be that the disappearance of pain in these circumstances is associated with the hypercapnia of congestive failure? In other conditions in which hypercapnia occurs, such as mitral stenosis and severe emphysema, angina pectoris is of rare occurrence. Such considerations serve to strengthen interest in the hypothesis that over-ventilation, hypocapnia, and alkalosis diminish the coronary flow of blood and predispose to angina pectoris.

In the course of ballistocardiographic studies, Brown[2] regularly observed an abnormally large respiratory variation in the amplitude of the ballistocardiograph in patients with angina pectoris. Such variations may be noted in the absence of angina but are of regular occurrence in the presence of angina. Many patients who had no angina when the respiratory variation of the ballistocardiograph was first observed, developed it later. When this respiratory variation was pronounced, breath-holding was found to result in improvement in the amplitude and definitiveness of the waves of the ballistocardiogram. It was also found that in some cases the ballistocardiograph could be improved and the tolerance for effort increased by the use of abdominal support in the manner described by William J. Kerr a number of years ago. One of the most striking instances of this sort was observed in a patient in whom angina developed following splanchnicectomy. Failures with this method were generally in cases in which there were varicose veins in the legs.

The significance of the foregoing observations is still far from clear. They have stimulated our interest in the widespread system of chemoreceptors, knowledge of which was recently well summarized by Pi-Suñer[7] and by Heymans.[5] Receptors of this type have long been known to exist in the arch of the aorta and in the carotid body, but others are found in the limbs, in the splanchnic areas, and in the entire respiratory tract from nose to alveoli. They send afferent impulses to the main respiratory centers and thus modify their activity. They are generally supposed to be stimulated by oxygen lack and moderate excess of carbon dioxide. They also exert some local circulatory effects; for instance, pulmonary vascular resistance is increased by lack of oxygen and moderate excess of carbon dioxide. It is an attractive hypothesis to suppose that stimuli causing over-ventilation originate in these receptors under circumstances in which the splanchnic and leg circulation is disturbed.

Let us now turn our attention to those phenomena which occur when ventilation is insufficient. One thinks at once of morphine narcosis, or poliomyelitis with involvement of the respiratory muscles. In both conditions severe anoxia may develop in association with carbon dioxide accumulation and acidosis.

Years ago Scott,[8] studying patients with *emphysema* of the lungs, observed that the addition of carbon dioxide to the inspired air did not increase

the volume of breathing to the same extent that it does in normal individuals. The full significance of this observation did not become apparent for a long time. I will attempt to sketch briefly the steps by which we have come to understand this phenomenon and the practical applications which we may make of our knowledge of its mechanism.

When a normal man is made anoxic, by ascent to high altitude, or by carbon monoxide poisoning, the effect is to stimulate the breathing to such an extent that carbon dioxide is lost in excess of production, and the blood becomes somewhat more alkaline, since the rate of carbon dioxide loss is greater than the rate at which the kidneys may excrete base in compensation. It appears that oxygen lack may increase sensitivity of the respiratory center to carbon dioxide, provided the respiratory center is not depressed by simultaneous carbon dioxide excess.

In an emphysematous person, owing to various mechanical factors, the elimination of carbon dioxide is less easy and a point is reached at which carbon dioxide may accumulate. This accumulation, if it develops slowly, is compensated by a gradual increase of base in the plasma and lymph, so that commonly in such instances there is an increase in the carbon dioxide combining power of the blood plasma, which may rise to rather high levels before a break in compensation occurs.

Experiments on animals, such as mice, showed that they may become acclimatized to prolonged residence in atmospheres containing excessive amounts of carbon dioxide; however, a point is reached at which carbon dioxide narcosis occurs with carbon dioxide acidosis. The narcotic effect of carbon dioxide diminishes the sensitivity of the respiratory center. When the mice were removed from this atmosphere, tetany usually developed owing to alkalosis, because the stored carbon dioxide was lost more rapidly than the base retained in compensation could be excreted (Seevers,[10] Miller[6]).

A patient with emphysema, who is compensated by an increased carbon dioxide combining power, is in equilibrium as far as the reaction of the blood is concerned. The pH of the plasma may be normal. This equilibrium may be easily upset, however. If one performs a Scott test[8] the addition of carbon dioxide to the inspired air does not increase the ventilation to the degree observed in normal persons, owing to the lessened sensitivity of the respiratory center to this stimulus. The gradual process by which compensation for carbon dioxide excess develops may go on so slowly that neither patient nor physician is concerned over it, until some intervening circumstance precipitates pulmonary failure. One of the commonest of such precipitating events is an attack of acute bronchitis. With fever and cough, cyanosis may become alarming, and orthopnea with asthmatic breathing may be noted, not infrequently with evidence of increased venous pressure and even edema. The patient becomes stuporous and confused. Respiration may become slower and shallower. If, at this point, oxygen is given by mask or nasal catheter, the patient may lapse into coma even though the cyanosis may be relieved. The optic discs may be choked. If oxygen administration is discontinued, partial consciousness may return with cyanosis.

Such a set of circumstances is well illustrated in the following observations in the case of a patient with obstructive emphysema. The hemoglobin content in the blood was 17.24 gm. per 100 cc. and the packed cell volume was 51 per cent of the whole blood. With the patient breathing room air, the oxygen saturation of the arterial blood was 69.9 volumes per cent and the carbon dioxide tension was 72 mm. of mercury. The pH of the blood was 7.3. After the patient had breathed pure oxygen for 15 minutes, cyanosis disappeared, the oxygen saturation reached 98.4 volumes per cent but the carbon dioxide tension rose to 87 mm. of mercury and the pH fell to 7.18, and the patient was totally unresponsive. The spinal fluid pressure while the patient was breathing room air was 160 mm. of water, but after 15 minutes of administration of oxygen by nasal catheter it was 260 mm. of water.

The phenomena in that case are typical of patients with pulmonary failure with hypercapnia, cyanosis and increased intracranial pressure, in which the administration of oxygen relieves the cyanosis but aggravates the carbon dioxide acidosis and narcosis, by further depression of the ventilation.

The correct management of such a situation has recently been pointed out by Boutourline-Young and Whittenberger,[1] who resuscitated such patients by the use of artificial respiration in an "iron lung." By increasing the ventilation of the patients the hypercapnia was relieved, the acidosis was corrected, and the sensitivity of the respiratory center was restored so that it again responded to its normal stimuli. Such treatment had the fortunate result that, once compensation was reestablished, the patients could maintain it for some time.

Application of this life-saving procedure is well illustrated by the case of a 71-year-old woman who had long-standing congestive failure associated with chronic cough and who had been admitted to the hospital on several occasions for chronic bronchitis and bronchopneumonia. Before she was admitted, weakness and mental confusion were noted. At the time of admittance the patient was semicomatose, cyanotic and orthopneic. Rhonchi were heard throughout both lungs. The heart was enlarged and there was pronounced accentuation of the second pulmonic sound. The edge of the liver

was palpated three fingers' breadth below the costal margin. Pitting edema was noted in dependent parts. Oxygen saturation of the arterial blood was only 55 per cent, the carbon dioxide tension was 91 mm. of mercury, and the carbon dioxide content was 32.9 millimoles per liter. After two days of administration of oxygen by nasal catheter the condition of the patient worsened. The pH of the arterial blood was 7.08. The patient was put in a Drinker respirator, against which she struggled, and death seemed imminent. However, with the introduction of an airway in the pharynx good ventilation was achieved and within an hour the patient became alert, the pH of the blood rose to 7.37, the arterial $pCO_2$ fell from 159 mm. to 82 mm. of mercury and the oxygen saturation reached 90 per cent. Two days after the patient was removed from the respirator, relapse occurred and she had to be returned to it. The carbon dioxide tension had risen to 210 mm. of mercury and the pH of the blood had decreased to 7.0. With artificial ventilation the carbon dioxide tension was rapidly reduced, the pH of the blood rose to 7.6 and tetany occurred. Gradually the situation was brought under control, but as difficulty was experienced in adjusting the ventilation, the patient was alternately alert, semi-comatose, alert and delirious. Gradual reduction in carbon dioxide content and tension of the arterial blood was achieved and the blood reaction brought into the range of normal. Penicillin was given throughout in order to control infection. The patient remained in the respirator for eleven days before the tension of gases in the blood and electrolyte content became normal.

In lung volume determinations a reduction in all partitions was noted. Cardiac catheterization showed the cardiac output to be normal. The mean pulmonary arterial pressure remained elevated at 26 mm. of mercury. The patient was discharged from the hospital and remained well for several months during which the arterial oxygen saturation was maintained at 89 per cent and the carbon dioxide tension ranged between 54 and 42 mm. of mercury.

The experiences with these two patients indicate that there are situations of everyday occurrence in practice which render the indiscriminate use of oxygen in high concentration somewhat hazardous. The instances in which it is disadvantageous to administer oxygen are those in which the compensation for chronic carbon dioxide retention has begun to fail and the respiratory center has diminished sensitivity to stimulation by inspired carbon dioxide, as determined by the Scott[8] test.

If one is confronted by a cyanotic patient in an emergency such that the facts concerning the tension and content of carbon dioxide in the blood are unknown, one should be quite alert in observing the effects of relieving the cyanosis by administration of oxygen. If clearing of the cyanosis is accompanied by a lapse into a deeper state of unconsciousness, it is indicative of primary failure of the ventilatory mechanism rather than of primary failure of the circulation. Continuation of the use of oxygen in such instances may be lethal, and further depression of ventilation by narcotics of the opium group should be carefully avoided. The aim of treatment should be first to eliminate the excessive carbon dioxide by increasing the ventilation by artificial respiration. The administration of oxygen should be undertaken gradually *after* there is evidence of improved sensitivity of the respiratory center.

When emphysematous patients with chronic pulmonary disease are under observation, the following phenomena may herald pulmonary or ventilatory insufficiency: (1) increasing elevation of the carbon dioxide combining power of the blood; progressive increase in the arterial carbon dioxide tension; (2) failure of carbon dioxide added to the inspired air to produce normal increase in pulmonary ventilation; (3) mental confusion deepening into stupor or into coma when cyanosis is relieved by administration of oxygen; (4) acceleration of circulation time before signs of congestive failure appear, or normal values for circulation time in patients with congestive failure.

It will be better for us to use the term *pulmonary insufficiency* or *ventilatory insufficiency* rather than *cor pulmonale* or *pulmonary heart disease.* If circulatory failure is mistaken for ventilatory failure, valuable time may be lost and harm done by using digitalis, morphine, and oxygen when the patient most urgently needs artificial increase in ventilation, aided by aminophyllin or bronchodilator drugs.

260 Crittenden Boulevard.

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# Phenylbutazone (Butazolidin) and Butapyrin®

## A Study of Clinical Effects in Arthritis and Gout

WILLIAM C. KUZELL, M.D., and
RALPH W. SCHAFFARZICK, M.D., San Francisco

*• A clinical evaluation of phenylbutazone and Butapyrin® (a mixture of phenylbutazone and aminopyrine) was made in 409 patients who had a variety of rheumatic diseases. Preliminary European claims were substantiated.*

*In gout a specific favorable effect was brought about by phenylbutazone alone.*

*Effects equivalent to the previously reported favorable response to Butapyrin (Irgapyrin) were observed when its constituent phenylbutazone was used alone. The drug had a suppressive effect in a high percentage of patients with rheumatoid arthritis, ankylosing spondylitis, arthritis with psoriasis and mixed arthritis (rheumatoid arthritis plus osteoarthritis). Favorable effect in peritendinitis of the shoulders, osteoporosis of the spine and acute lumbosacral strain also was noted.*

*Toxicity resulted in discontinuance of medication in 10 per cent of patients with each drug. Manifestations of toxicity generally included fluid retention, nausea and rash, but there were several instances of transitory leukopenia and anemia. There was one instance of agranulocytosis with Butapyrin but none with phenylbutazone.† Aggravation of peptic ulcer occurred in ten patients with hemorrhage in two. Generally the toxicity was of a low order as compared with that of other drugs having an antirheumatic effect.*

† See Addendum.

PHENYLBUTAZONE (butazolidin or 3, 5-dioxo-1, 2-diphenyl-4-n-butylpyrazolidine, a pyrazole derivative) was synthesized by chemists of the J. R. Geigy Company of Basle.* Its first clinical application was in mixture in equal parts with aminopyrine (Figure 1). This mixture is known as Irgapyrin® in Europe and as Butapyrin® in this country. In extensive European clinical trials in rheumatic diseases, with favorable results, the mixture was given parenterally.[1] Since aminopyrine, although widely used clinically for many years, has no known antirheumatic effect, it was felt desirable to evaluate the constituent compound, phenylbutazone, alone. At the request of the authors this substance was made available for parenteral and oral use.. The original work using the mixture resulted from the discovery that phenylbutazone promoted solubility of the relatively insoluble aminopyrine. Preliminary clinical trials by the authors confirmed in a general way the claims of the European investigators. Further, since it was observed that Butapyrin apparently had specific effect in acute gout, repetition of the work using phenylbutazone alone seemed to be indicated. Another purpose was to reevaluate the original claims in accord with the diagnostic and therapeutic criteria of the American Rheumatism Association, so that comparison of the antirheumatic activity of these substances could be made with that of other agents currently used in treatment of rheumatic diseases. Since there was no accepted system of classification and rating for the therapeutic effect of medications in gout, it was necessary to devise and employ such a system, which is described below. In a preliminary report[4] it was noted that phenylbutazone used alone had the same specific effect in gout that had previously been observed with Butapyrin, and that there was also an antirheumatic effect beyond simple analgesia following its use.

From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco.

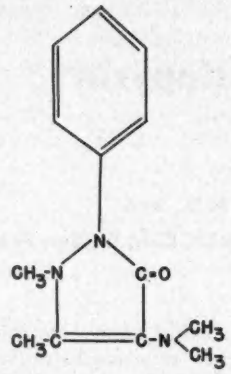
Presented before the Section on General Medicine at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

* Phenylbutazone and Butapyrin were supplied by Geigy Pharmaceuticals, 220 Church Street, New York, N. Y.

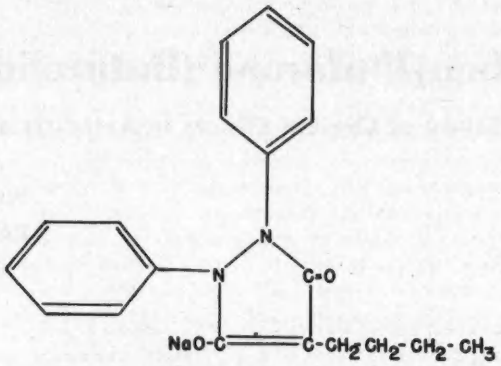
### PHARMACOLOGY

Pharmacological investigation by Wilhelmi indicated that phenylbutazone raises the pain threshold to electrical stimulation of pulp of incisor teeth in rabbits, that it has an antipyretic effect in rabbits infected with *Escherichia coli*, and that it delays the development of erythema on the skin of rabbits exposed to ultraviolet irradiation.[1]

Phenylbutazone was found to be more effective than aminopyrine or Butapyrin in inhibiting localized edema and increased capillary permeability pro-



4-DIMETHYLAMINO-1-PHENYL-2,3-DIMETHYL-PYRAZOLON
(DIMETHYLAMINOANTIPYRIN = AMINOPYRINE)



3,5-DIOXO-1,2-DIPHENYL-4-N-BUTYL-PYRAZOLIDIN SODIUM (G 13871)

Figure 1.—Structural Formulae of Aminopyrine and Phenylbutazone (Butazolidin).

duced by the application of irritants such as croton oil.[1] Studying the blood concentrations, Pulver[1] found that phenylbutazone is excreted at a slower rate than is aminopyrine. In the mouse and rat, the $LD_{50}$ of phenylbutazone is lower than that of either aminopyrine or of the mixture Butapyrin. In large doses, these compounds produce tonic-clonic convulsions. In rats, the daily oral administration of phenylbutazone, 50 mg. per kilogram of body weight, was found to produce no apparent chronic toxicity. None of these compounds stimulates the adrenal cortex directly in hypophysectomized rats;[4] whereas, aminopyrine and Butapyrin appear to stimulate the anterior pituitary to release corticotropin. Phenylbutazone alone had no such effect. In experiments by the authors, none of the compounds was capable of maintaining the adrenal glands of hypophysectomized rats. In tissue respiration studies, it was observed that phenylbutazone depressed the oxygen consumption of rat cerebral cortex. The effect of these compounds on rat polyarthritis produced by pleuropneumonia-like organisms also was studied. While aminopyrine was found to cause a slight reduction in the extent of this specific experimental arthritis as compared with the controls, phenylbutazone produced a slight aggravation of the arthritis, as had corticotropin (ACTH), cortisone acetate and Compound F acetate.[5] No significant changes were noted in the cell content of the blood of animals that were given these pyrazoles for long periods.

#### CLINICAL EVALUATION

Clinical study of 409 patients who received Butapyrin and/or phenylbutazone was carried out. Butapyrin was administered orally in coated tablets containing 250 mg. of the mixture, and intramuscularly as a 30 per cent solution containing equal parts of aminopyrine and the sodium salt of butazolidin. Phenylbutazone was available in coated tablets containing either 125 or 200 mg., and in 20 per cent solution of the sodium salt. The range of the oral dosage was approximately the same for both substances, varying between 250 and 1,500 mg. daily. In most instances intramuscular dosage did not exceed a daily total of 1.5 gm., although occasionally twice that amount was given. Parenteral administration was reserved for acute situations, in which rapid symptomatic relief was desirable. Intravenous administration was not employed, although European investigators have reported intravenous use of Butapyrin. The period of clinical observation for Butapyrin was 19 months. During the last ten months of the period of this study, however, phenylbutazone was used almost exclusively. It was possible to compare the effect of the two substances in many patients with chronic or recurrent disease; and occasionally placebos were substituted. Placebos were found to be universally ineffective.

*Gout:* In Table 1 the therapeutic response of 65 patients to Butapyrin and of 74 patients to phenylbutazone is presented. The system for rating this response and classifying the patients is described in that table. Criteria for the diagnosis of gout were: History of acute painful joint swelling of rapid onset followed by complete remission with tendency to recurrence following various kinds of stress; the presence of hyperuricemia; characteristic roentgenographic "punched-out" areas in the subjacent bony cortex of the affected articulations; increased urinary excretion or uric acid; presence of tophi; and characteristic response to colchicine. Obviously since some of the patients were in the pretophaceous stage, not all of the criteria were fulfilled in every case. It is perhaps noteworthy that among the total

**TABLE 1.—*Therapeutic Response of Gout to Butapyrin (BP) and Phenylbutazone (PB)***

| *Stage | Number of Patients with Various Grades of Response† I BP | I PB | II BP | II PB | III BP | III PB | IV BP | IV PB |
|---|---|---|---|---|---|---|---|---|
| I | 17 | 10 | 6 | 5 | 1 | 1 | 0 | 0 |
| II | 13 | 25 | 16 | 24 | 11 | 9 | 1 | 0 |
| Totals | 30 | 35 | 22 | 29 | 12 | 10 | 1 | 0 |

*Stage I. Acute gout, with asymptomatic periods between exacerbations. Stage II. Acute gout superimposed upon chronic gouty arthritis.

†Therapeutic Response: Grade I. Complete remission in 48 hours or less. Grade II. Major improvement, indicating rapid decrease of signs and symptoms within 48 hours, but with slight persistence up to seven days following initial therapy. Grade III. Minor improvement with analgesia and decreased swelling, but not complete remission, in spite of continued therapy. Grade IV. No effect.

**TABLE 2.—*Therapeutic Response of Rheumatoid Arthritis to Butapyrin and Phenylbutazone***

| Stage | Class | Grade of Response Number of Patients I BP | I PB | II BP | II PB | III BP | III PB | IV BP | IV PB |
|---|---|---|---|---|---|---|---|---|---|
| I | I | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | II | 1 | 0 | 1 | 5 | 2 | 4 | 0 | 2 |
| | III | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| | IV | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| II | I | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | II | 3 | 1 | 8 | 12 | 5 | 4 | 0 | 1 |
| | III | 1 | 0 | 7 | 6 | 2 | 1 | 2 | 0 |
| III | II | 1 | 1 | 1 | 0 | 1 | 0 | 2 | 1 |
| | III | 0 | 0 | 3 | 4 | 1 | 2 | 2 | 0 |
| IV | II | 1 | 0 | 2 | 3 | 2 | 2 | 0 | 1 |
| | III | 0 | 0 | 3 | 4 | 6 | 4 | 4 | 1 |
| | IV | 0 | 0 | 0 | 0 | 2 | 5 | 2 | 0 |
| Totals | | 7 | 5 | 26 | 35 | 21 | 22 | 12 | 6 |

According to the criteria of the American Rheumatism Association[2]:

Stage: Extent of rheumatoid progression, objective changes increasing from mild (I) to severe (IV).

Class: Functional capacity of the patient, ranging from complete activity (I) to incapacitation (IV).

Grade: Response of rheumatoid activity to therapy, ranging from complete remission (I) to complete lack of effect (IV).

BP = Butapyrin, 66 patients.

PB = Phenylbutazone, 68 patients.

of 107 gouty patients in this series 27 were females, all save one of them postmenopausal.

All patients treated with phenylbutazone had some degree of clinical response. Approximately half of them had complete clinical remission in 48 hours or less, and 84 per cent became asymptomatic within one week after institution of therapy. With Butapyrin the results were of the same order; 80 per cent of the patients had a similar degree of therapeutic response. One of the 65 patients treated with Butapyrin had no improvement. He had moderately severe diabetes in addition to gout, and later he had minor improvement when treated with phenylbutazone.

Although the uric acid values in the serum promptly decreased following the use of either Butapyrin or phenylbutazone, there was no consistent increase in the urinary excretion of uric acid coincident with decrease in serum uric acid—a phenomenon which deserves further study.

Of the 107 gouty patients, 32 received both Butapyrin and phenylbutazone at different times. Twenty-two had equivalent results with either drug, four responded better to Butapyrin, and six to phenylbutazone. In three patients who obtained partial relief from the pyrazoles, cortisone and/or corticotropin were superior. All except one of 68 patients who previously received colchicine felt better when given either Butapyrin or phenylbutazone than they had when treated with colchicine and/or salicylates. In no instance was the gout apparently aggravated by the pyrazoles. Treatment was continued generally for one week following subsidence of symptoms in acute exacerbations, but in 36 patients with chronic gouty arthritis maintenance therapy was employed. Twenty-seven of the 36 had decreased frequency of acute attacks as well as amelioration of the chronic gouty arthritis. Acute exacerbations in patients with chronic disease responded to increased dosage. The maintenance dose varied from 200 to 800 mg. daily.

*Rheumatoid Arthritis:* Among 97 patients treated (Table 2), 37 received both Butapyrin and phenylbutazone. Thirty of the 37 had equivalent response to both drugs, four had better results from Butapyrin and three from phenylbutazone. Twelve of the 66 patients treated with Butapyrin and six of the 68 patients treated with phenylbutazone had no therapeutic response; but none was made worse. On the other hand, 33 of 66 treated with Butapyrin and 40 of 68 given phenylbutazone therapy had major improvement which persisted as long as the medication was continued. Within five days after discontinuance of therapy, symptoms returned in all instances. One-third of the patients in both groups had only minor improvement, chiefly characterized by analgesia. Fifteen patients had a greater degree of improvement when treated with cortisone and/or corticotropin than when either Butapyrin or phenylbutazone therapy was given, while five others were equally comfortable whether treated with the hormones or the pyrazoles. While in no case was Butapyrin or phenylbutazone superior to cortisone or corticotropin, the incidence of undesirable side effects was greater with the hormones. In several patients cortisone acetate and phenylbutazone were used alternately, each for a period of two weeks, with satisfactory results. In these instances patients generally felt stronger while taking cortisone acetate.

*Ankylosing Spondylitis* (rheumatoid arthritis of the spine): Thirty-five patients were treated (Table 3). Eight of the twelve patients who received both Butapyrin and phenylbutazone had equivalent response to both drugs, three had better response to phenylbutazone, and one to Butapyrin. Major improvement was noted in 15 of 26 patients treated with Butapyrin and in 17 of 21 who were given

**TABLE 3.—*Therapeutic Response of Ankylosing Spondylitis to Butapyrin and Phenylbutazone***

| Stage | Class | Grade of Response—Number of Patients I BP | I PB | II BP | II PB | III BP | III PB | IV BP | IV PB |
|---|---|---|---|---|---|---|---|---|---|
| II | II | 1 | 0 | 2 | 4 | 3 | 1 | 3 | 0 |
| | III | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 |
| III | II | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 0 |
| | III | 0 | 1 | 3 | 1 | 0 | 0 | 0 | 0 |
| IV | II | 0 | 0 | 3 | 1 | 0 | 1 | 1 | 0 |
| | III | 1 | 0 | 4 | 7 | 0 | 0 | 0 | 0 |
| | IV | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Totals | | 2 | 1 | 13 | 17 | 5 | 3 | 6 | 0 |

For interpretation, see Table 2.
BP = Butapyrin, 26 patients.
PB = Phenylbutazone, 21 patients.

**TABLE 4.—*Therapeutic Response of Mixed Rheumatoid and Osteoarthritis to Butapyrin and Phenylbutazone***

| Stage | Class | Grade of Response—Number of Patients I BP | I PB | II BP | II PB | III BP | III PB | IV BP | IV PB |
|---|---|---|---|---|---|---|---|---|---|
| II | I | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | II | 0 | 0 | 4 | 12 | 3 | 9 | 3 | 7 |
| | III | 0 | 0 | 1 | 3 | 0 | 1 | 0 | 2 |
| III | II | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | III | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| IV | II | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | III | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Totals | | 0 | 0 | 6 | 18 | 4 | 10 | 4 | 10 |

For interpretation, see Table 2.
BP = Butapyrin, 14 patients.
PB = Phenylbutazone, 38 patients.

**TABLE 5.—*Therapeutic Response of Arthritis with Psoriasis to Butapyrin and Phenylbutazone***

| Stage | Class | Grade of Response—Number of Patients I BP | I PB | II BP | II PB | III BP | III PB | IV BP | IV PB |
|---|---|---|---|---|---|---|---|---|---|
| II | II | 0 | 0 | 1 | 0 | 4 | 2 | 0 | 1 |
| | III | 0 | 0 | 2 | 2 | 1 | 1 | 0 | 0 |
| III | II | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| IV | II | 0 | 0 | 1 | 3 | 1 | 0 | 0 | 0 |
| Totals | | 0 | 0 | 4 | 5 | 7 | 4 | 0 | 1 |

For interpretation, see Table 2.
BP = Butapyrin, 11 patients.
PB = Phenylbutazone, 10 patients.

phenylbutazone. Six of the patients who received Butapyrin had no response to it. Phenylbutazone afforded some measure of improvement in all cases in which it was used. Twenty of the 35 patients received both x-ray therapy and the drugs. Five of them had greater response to irradiation than to either drug, but in nine cases the drugs were superior and in six others there was a similar degree of improvement. In two cases cortisone was used and the response was inferior to that of the pyrazoles, since one of the patients became psychotic during cortisone therapy and the other suffered activation of quiescent pulmonary tuberculosis.

**TABLE 6.—*Therapeutic Response of Miscellaneous Disorders to Butapyrin and Phenylbutazone***

| Disorder | Degree of Improvement—Number of Patients Major BP | Major PB | Minor BP | Minor PB | None BP | None PB |
|---|---|---|---|---|---|---|
| Peritendinitis, shoulder | 10 | 5 | 6 | 2 | 3 | 0 |
| Osteoarthritis | 4 | 10 | 3 | 2 | 6 | 6 |
| Osteoporosis | 3 | 9 | 1 | 3 | 0 | 2 |
| Malum coxae senilis | 1 | 1 | 6 | 3 | 0 | 0 |
| Total | 18 | 25 | 16 | 10 | 9 | 8 |

BP = Butapyrin, 43 patients.
PB = Phenylbutazone, 43 patients.

*Mixed Rheumatoid and Osteoarthritis:* Of 45 patients (Table 4) with concomitant rheumatoid and osteoarthritis (degenerative joint disease), eight received both Butapyrin and phenylbutazone. Butapyrin was superior in three cases, phenylbutazone in three, and in two the response was similar. The improvement was less in the group of patients with mixed disease than in the group with rheumatoid arthritis only; none of the patients had Grade I therapeutic response and more than half of them had only minor improvement or none at all.

*Psoriasis with Arthritis:* Thirteen patients with psoriasis and arthritis were treated and eight received both drugs (Table 5). Seven of the eight had equivalent response to both drugs, while one had better response to phenylbutazone. Although none of the patients had Grade I response with either drug, all of those treated with Butapyrin were benefited, and all but one of those given phenylbutazone had some measure of symptomatic relief. Dermal lesions of seven of the patients cleared during therapy although no local medication was used.

*Miscellaneous Disorders* (Table 6): Twenty-two patients with acute or subacute peritendinitis of the shoulders were treated. Four of them received both agents with equivalent response. Sixteen of 19 treated with Butapyrin and all of seven treated with phenylbutazone made a good therapeutic response, which was in most instances complete within two days. In all cases medication was withdrawn without recurrence of symptoms.

Of 29 osteoarthritic patients treated, two received both agents with similar degree of improvement. Twelve of 18 who were treated with phenylbutazone had some measure of relief, as did seven of 13 who were given Butapyrin.

Fourteen patients with postmenopausal or presenile osteoporosis of the spine were treated. Four who were treated first with one of the drugs then the other had equivalent relief from both. Four patients treated with Butapyrin and 12 of 14 treated with phenylbutazone, quickly had some relief of pain and spasm in the back while appropriate hormone therapy was being instituted.

Three of eight patients with *malum coxae senilis* had similar response to both drugs and all had

TABLE 7.—*Toxic Manifestations of Butapyrin*

| Disorder | No. Patients Treated | Manifestations: Rash | Edema | Nausea | Ulcer Aggravation | Anemia | Leukopenia | Agranulocytosis | Stomatitis | Vertigo | Nervousness | No. Patients showing toxicity | Drug Discontinued due to toxicity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gout | 64 | .... | 5 | 5 | .... | .... | .... | .... | .... | .... | .... | 9 | 2 |
| Rheumatoid arthritis | 66 | 3 | 6 | 4 | 1 | 3 | 2 | .... | .... | .... | .... | 14 | 8 |
| Ankylosing spondylitis | 26 | .... | 2 | 2 | 1 | .... | .... | .... | .... | .... | .... | 5 | 2 |
| Mixed arthritis | 14 | .... | 3 | 1 | 1 | .... | .... | 1 | .... | .... | .... | 6 | 4 |
| Psoriasis with arthritis | 11 | 1 | .... | 1 | 1 | .... | .... | .... | .... | .... | .... | 2 | 1 |
| Osteoarthritis | 13 | .... | .... | 1 | .... | .... | .... | .... | .... | 1 | .... | 2 | 0 |
| Malum coxae senilis | 7 | .... | 2 | .... | 1 | .... | .... | .... | .... | 1 | .... | 4 | 0 |
| Osteoporosis | 4 | .... | 2 | .... | .... | .... | .... | .... | .... | .... | .... | 2 | 0 |
| Peritendinitis, shoulder | 19 | 1 | 1 | 2 | 2 | .... | .... | .... | .... | .... | .... | 5 | 4 |
| Peripheral vascular disease | 5 | .... | .... | .... | .... | .... | .... | .... | .... | .... | .... | 0 | 0 |
| Miscellaneous | 18 | 1 | 2 | 2 | .... | .... | .... | .... | .... | .... | .... | 4 | 3 |
| Totals | 247 | 6 | 23 | 18 | 7 | 3 | 2 | 1 | 0 | 2 | 0 | 53 | 24 |

some relief from pain and stiffness, but in no instance was there more than minor objective improvement.

Therapeutic trials were made in peripheral vascular disorders, since it was noted, in treating arthritic patients, that warming of the extremities often occurred within a few minutes after parenteral administration of either agent. One patient with severe Raynaud's disease had complete relief of symptoms, but owing to fluid retention she was unable to tolerate prolonged medication. One patient with thromboangiitis obliterans had pronounced relief and another had minor improvement. Both were able to walk greater distances without claudication.

Four patients with advanced arteriosclerosis of the leg vessels were given satisfactory analgesia; but no improvement in oscillometric readings was observed.

Three patients with multiple sclerosis experienced no relief during pyrazole therapy. Three patients with disseminated lupus erythematosus and six with idiopathic migraine headache were unrelieved. Pain associated with acromegaly was not altered in one patient. In another, generalized atopic dermatitis was aggravated by Butapyrin. Three of four patients with acute myofibrositis had relief of pain and spasm within several hours of parenteral administration of Butapyrin or phenylbutazone.

Five of nine patients with nerve root pain from herniation of nucleus pulposus received satisfactory temporary analgesia, but four were totally unrelieved. Two children with juvenile rheumatoid arthritis improved when treated with phenylbutazone (one had Grade II and the other Grade III therapeutic response).

### CLINICAL TOXICITY

Of 247 patients treated with Butapyrin, 53 had toxic side effects, which in 24 instances (10 per cent) were serious enough to warrant discontinuance of medication (Table 7). There were 62 toxic manifestations observed among the 53 patients. Most frequently seen were edema and nausea. There was one case of agranulocytosis with recovery after discontinuance of medication. Two instances of transitory leukopenia (leukocytes fewer than 3,000 per cubic millimeter) and three cases of anemia (hemoglobin less than 10 gm. per 100 cc.) were observed. Morbilliform rash occurred in six patients and aggravation of peptic ulcer in seven others.

There were 84 toxic manifestations in 64 of 278 patients who received phenylbutazone; and in 28 cases therapy was discontinued because of toxicity (Table 8). The incidence of rash was 4.3 per cent and, as with Butapyrin, edema and nausea were the most common toxic effects. There were two instances of purpura and three of stomatitis but none of agranulocytosis.

The edema occurring during the use of either drug subsided within three to five days after discontinuance of therapy, or with institution of sodium restriction. Mercurial diuretics were generally ineffective in ameliorating the fluid retention produced by these pyrazoles.

The nausea was usually associated with oral administration and often could be reduced or avoided by the concurrent use of antacids. However, as nausea was observed during parenteral administration in several instances, a central nauseant effect may be involved.

The incidence of toxic reactions appeared to be lowest among the patients with gout and highest among those with mixed rheumatoid and osteoarthritis.

Although the incidence of hematopoietic damage appeared to be low and the changes transitory, the blood was examined at weekly or bi-weekly intervals in most instances.

There was no evidence of altered renal function and in no case was coexisting diabetes demonstrably intensified.

TABLE 8.—*Toxic Manifestations of Phenylbutazone*

| Disorder | No. Patients Treated | Manifestations: Rash | Edema | Nausea | Ulcer | Anemia | Leukopenia | Stomatitis | Vertigo | Nervousness | Purpura | G.I. Hemorrhage | No. Patients showing toxicity | Drug discontinued due to toxicity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gout | 76 | 2 | 4 | 6 | 0 | 0 | 0 | 1 | .... | 1 | .... | .... | 9 | 4 |
| Rheumatoid arthritis | 68 | 4 | 4 | 10 | 0 | 1 | 1 | 1 | 1 | .... | .... | .... | 15 | 4 |
| Ankylosing spondylitis | 21 | 1 | 1 | 2 | .... | .... | .... | .... | .... | 1 | .... | .... | 4 | 1 |
| Mixed arthritis | 38 | 2 | 6 | 4 | 1 | .... | 1 | 1 | .... | .... | 1 | .... | 13 | 8 |
| Psoriasis with arthritis | 10 | .... | .... | 2 | .... | .... | .... | .... | .... | .... | .... | 1 | 2 | 1 |
| Osteoarthritis | 16 | 1 | 1 | 6 | 0 | .... | .... | .... | 0 | .... | 1 | .... | 8 | 4 |
| Malum coxae senilis | 4 | .... | 2 | .... | 1 | .... | .... | .... | .... | .... | .... | 1 | 3 | 0 |
| Osteoporosis | 14 | .... | 2 | .... | .... | 1 | .... | .... | .... | .... | .... | .... | 3 | 0 |
| Peritendinitis, shoulder | 7 | .... | 2 | 1 | 1 | .... | .... | .... | .... | .... | .... | .... | 3 | 3 |
| Peripheral vascular disease | 4 | .... | 1 | .... | .... | .... | .... | .... | .... | .... | .... | .... | 1 | 1 |
| Miscellaneous | 18 | 2 | 1 | .... | .... | .... | .... | .... | .... | .... | .... | .... | 3 | 2 |
| Totals | 278 | 12 | 24 | 31 | 3 | 2 | 2 | 3 | 1 | 2 | 2 | 2 | 64 | 28 |

Since these drugs possess antipyretic and analgesic properties, patients in whom respiratory infections developed during therapy often experienced only mild weakness and diaphoresis rather than the usual more severe symptom complexes.

Sulfobromphthalein tests of liver function and determinations of platelet content of the blood were carried out during pyrazole therapy in twelve cases. There was no departure from normal in either respect. Although no studies of blood volume were done, the rapid development of edema may have resulted in transitory reduction of hemoglobin values due to hemodilution.

## DISCUSSION

Although the original European clinical studies were made with a mixture, Butapyrin (phenylbutazone plus aminopyrine), subsequent observations by the authors established the important therapeutic effect of phenylbutazone used alone. The present comparative study shows that there is no significant difference in the therapeutic response to Butapyrin and phenylbutazone in gout and a variety of rheumatic diseases.

Phenylbutazone effects the same degree of beneficial action as Butapyrin in gout.[2] Although aminopyrine once was widely used clinically no reference could be found in the available literature concerning its use in gout. The pronounced favorable response of gout to phenylbutazone exceeded that to colchicine in all the cases where comparison was made by the authors. Although at present there is no evidence to indicate that phenylbutazone promotes the excretion of urates, the uniformly striking reduction of uric acid content in the blood would suggest that the action of the drug in gout is indeed specifically concerned with the metabolism of urates.

The antirheumatic effect of these agents in rheumatoid arthritis, in psoriasis with arthritis, in mixed arthritis, and in ankylosing spondylitis, *depends on continued administration* of the medication. In ankylosing spondylitis the therapeutic response is perhaps slightly better than in rheumatoid arthritis and in the other related diseases previously mentioned. This appears to be particularly true with regard to phenylbutazone, which had beneficial effect of some degree in all cases of ankylosing spondylitis.

The temporary use of these agents in osteoporosis of the spine, peritendinitis of the shoulder, and acute fibromyositis is apparently of considerable value.

The most important manifestations of the toxicity of the two agents were fluid retention, nausea, rash, and aggravation of peptic ulcer. Therapy had to be discontinued in only 10 per cent of patients with each preparation. However, in gout, where the greatest measure of benefit was observed, it was necessary to discontinue therapy in only 3 per cent of patients receiving Butapyrin and 5 per cent of those treated with phenylbutazone.

Although there was one case of agranulocytosis owing to Butapyrin, the patient recovered. The occurrence of two instances of leukopenia and three of anemia in the group receiving Butapyrin included one male with monocytic leukemia who had both leukopenia and anemia. Another male who later died of lymphosarcoma had anemia while receiving Butapyrin, but this could have been the result of pulmonary hemorrhage. Among patients treated with phenylbutazone alone, two transitory instances of leukopenia were observed and there were two patients with anemia, one of whom was the previously mentioned patient who had monocytic leukemia. The phenylbutazone was continued in these patients. One received a transfusion of whole blood and all three received supplemental liver extract and iron by mouth. The blood returned to normal in each in-

stance. The occurrence of gastrointestinal hemorrhage in two patients during phenylbutazone therapy was presumably owing to aggravation of peptic ulcer. One of these patients successfully resumed the medication by mouth and the other intramuscularly together with appropriate ulcer therapy.

#### ADDENDUM

Since the time of presentation of this paper two cases of agranulocytosis have occurred among patients treated with phenylbutazone. There were two other cases of agranulocytosis among a group of patients treated with phenylbutazone and acetosulfone concurrently. After recovery from agranulocytosis both patients who received acetosulfone and one of the other two were given phenylbutazone again, without ill effect. This suggests that the depression of the granulocytes was owing, not to hypersensitivity, but to direct depression. Therefore, when phenylbutazone is used concurrently with other drugs that might cause bone marrow depression, extreme caution is necessary.

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# Third Degree Laceration at Delivery

## Etiological Considerations, and a Technique for Repair

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• *In a series of 14,080 cases in which either median or mediolateral episiotomy was used to facilitate delivery, third degree extension occurred in 75 cases (0.5 per cent). In related data extension of laceration was observed to occur in an inordinately high proportion of cases in association with use of forceps, greater than normal anterior pelvic depth, delivery of a large baby, primiparity, abnormal position and presentation, use of median incision (although extension also occurred in some cases in which mediolateral episiotomy was done), and hyperflexion and extreme abduction of the thighs.*

*The method of immediate postpartum repair employed was associated with a minimal amount of postpartum discomfort, and late complications were almost nil.*

RECENT REPORTS indicate a gradual but positive trend in this country toward routine employment of median episiotomy in vaginal delivery. Eastman[1] stated that median episiotomy is a satisfactory procedure in nine out of ten deliveries. Kaltreider and Dixon[2] after extensive review of cases concluded that median episiotomy is suitable in 93 per cent of deliveries. It may be anticipated that with such teaching now appearing in standard texts, median incision will come to be used almost exclusively in obstetric care. As it is inevitable that third degree laceration will occasionally occur in cases in which median episiotomy is carried out, consideration of the causes and the repair of such lesions comes to the fore.

Study was made of 75 cases of third degree laceration that occurred in a total of 14,080 patients in whom episiotomy (either median or mediolateral) was done during the period January 1, 1946, to January 1, 1951 (see Table 1). The incidence of third degree laceration was 0.5 per cent. The attending physicians were a mixed group—residents, nonspecialists and specialists.

Seven of the 75 patients were between 15 and 20 years of age, 48 were between 20 and 30, and 20 were between 30 and 40. As fecundity is usually associated with the third and fourth decades of life, the age of the patient did not appear to be an important factor relative to the occurrence of third degree laceration.

Sixty-one of the patients were primiparae and 14 multiparae, as would be expected in light of the lesser distensibility of pelvic tissues in primiparae.

The average duration of labor was ten hours, the longest 27 hours, and the shortest 31 minutes. Although it is logical to expect rectal injuries in cases of prolonged labor, which often causes edema and friability of tissues and is associated with difficult delivery, the incidence of lacerations in this series cannot be explained on that basis, in view of the relatively short average period of labor.

**TABLE 1.—*Median and mediolateral episiotomy in a series of 14,080 cases***

| Episiotomy | No. | Per cent of series |
|---|---|---|
| Median | 6,577 | 47 |
| Mediolateral | 7,503 | 53 |
| Total | 14,080 | 100 |

Note: Third degree extension occurred in 75 cases (0.5 per cent).

Presented before the Section on Obstetrics and Gynecology at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

**TABLE 2.—*Fetal position***

| | | |
|---|---|---|
| Occiput anterior | | 62 |
| Occiput posterior: | | |
| Kielland rotation | 3 | |
| Manual rotation | 3 | |
| Occiput posterior as such | 2 | |
| Total occiput-posterior | | 8 |
| Breech presentation | | 5 |

The occiput posterior is said to occur in 20 per cent of all deliveries and breech presentation in 4 per cent. When the incidence of third degree extension associated with these positions in this series (Table 2) is viewed in light of the fact that third degree laceration occurred in only 0.5 per cent of all cases in the series, it is obvious that fetal position was an etiologic factor.

As forceps were used in 62 of the 75 cases (a high proportion) the use of forceps must be indicted as an etiological factor in third degree lacerations.

While it was to be expected that extension of laceration would occur relatively often when median episiotomy was carried out, there was also a fairly high incidence of third degree extension associated

with mediolateral episiotomy, a procedure used to avoid rectal injury. In 59 of the 75 cases median episiotomy was used, in 12 mediolateral. Episiotomy was not done in four cases in which third degree laceration occurred.

**TABLE 3.—*Weight of babies in cases of rectal laceration in present series, as compared with general average incidence of babies of each size***

| Grams | Associated with rectal laceration (per cent) | Average clinic incidence (per cent) |
|---|---|---|
| 2268-2722 | 7.0 | 6.4 |
| 2722-3175 | 17.3 | 16.3 |
| 3175-3629 | 33.2 | 44.7 |
| 3629-4082 | 22.6 | 30.6 |
| 4082-4536 | 17.3 | 1.6 |
| 4536-4990 | 2.6 | .4 |

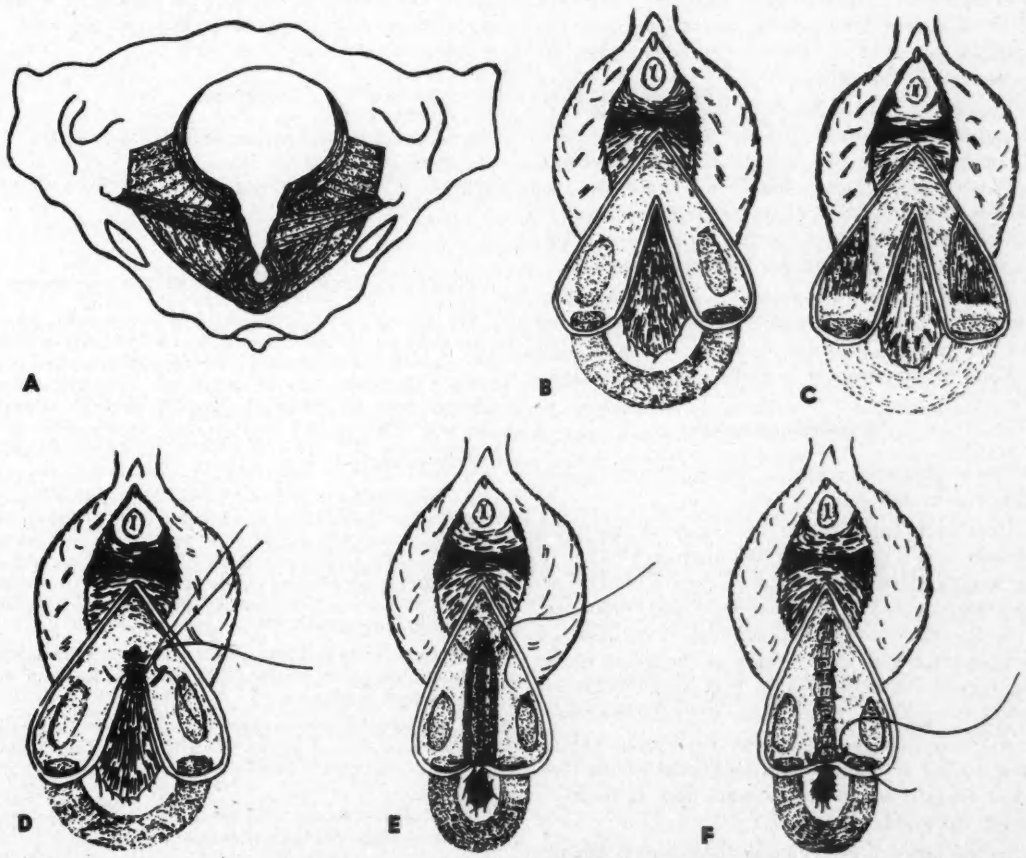
Large babies were associated with third degree laceration in a significant number of cases (Table 3).

General anesthesia was used in 13 cases and spinal anesthesia in 62, but it cannot be concluded from that fact that spinal anesthesia is an etiological factor in third degree laceration, for spinal anesthesia was employed in the majority of deliveries surveyed in this study.

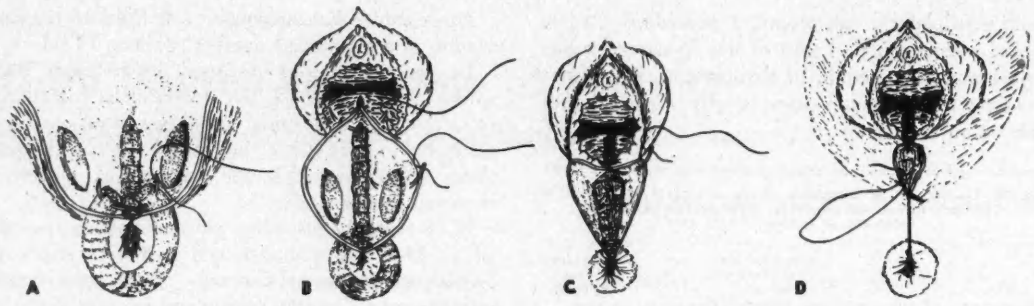
In 58 cases the attending physician was a specialist, in 13 a non-specialist, and in four a resident. These data are indicative only of the widespread employment of median episiotomy by specialists.

### MISCELLANEOUS FACTORS

*Anterior Pelvic Depth.* From a mechanical standpoint it is apparent that if the anterior pelvic depth




*A*, diagrammatic illustration of the muscle structures involved in third degree laceration. *B*, the tissues to be repaired. Note the prominence of the severed deep transverse perineal muscles which are often mistaken for the sphincter ani. *C*, taken from a drawing in Greenhill's text, purports to show the presence of the exposed levator muscles indicated by X. Actually, however, the levators lie too far laterally to be seen in median episiotomy. It is the fascia covering the levators that is visible, and it is this structure alone that is reapproximated in the repair. *D*, the repair is commenced at the apex of the rectal laceration with interrupted sutures. The first layer goes through only the serosa, muscularis and submucosa of the rectum to bring about inversion of the edges. Suturing is carried down to the anal pillars. *E*, a second layer of interrupted sutures is started just above the apex of the first layer and includes the perirectal fascia and a portion of the fascia of the rectovaginal septum. *F*, the second layer is carried past the anal margin to the skin of the perineum.




**After the rectal wall has been repaired in two layers, the cut ends of the sphincter ani are grasped with two Allis clamps. Then, *A*, two or three mattress-type sutures are used to approximate the severed ends, with care taken to include only the fascial sheath and peripheral portions of the sphincter ani, since sutures through the muscle body produce painful spasm of the muscle. *B*, similar approximation of the cut ends of the deep transverse perineal muscles. *C*, approximation of the superficial fascia. *D*, subcuticular closure of the skin.**

is greater than normal there is increased likelihood of third degree extension of laceration, since the posterior segment of the pelvic outlet must be opened wider for delivery.

*Position of Legs in Stirrups.* When the thighs are placed in extreme abduction and hyperflexed on the abdomen, the skin and superficial fascia are drawn tight over the perineum, which causes anterior displacement and fixation of the rectum. Concomitant with the loss of elasticity of the perineum is an increased tendency toward third degree extension.

*Type of Forceps Employed.* It would seem that use of forceps having a wide separation of opposing shanks, such as Simpson forceps, entails greater liability of extension of laceration into the rectum.

#### TECHNIQUE OF REPAIR

The technique of repair of laceration used by the author is as follows:

Upon completion of the third stage of labor, the patient is redraped and a thorough inspection of the vagina and cervix is made. Often a button-hole opening into the rectum is noted on rectal palpation. This is converted into a complete laceration. A Gelpi retractor is put in place at the mucocutaneous junction of the vaginal orifice. No. 000 chromic catgut is employed throughout. (See illustrations.)

After operations all patients are treated exactly as a normal puerpera would be treated except that, when enemas are given, extreme care is taken to direct the nozzle posteriorly.

In the series here reviewed there was a slightly higher morbidity rate than is associated with cases in which third degree laceration does not occur, but in none of the three cases in which this reaction did develop was it directly attributable to perineal infection.

The most common complication, secondary anemia of moderate to severe degree, occurred in 16 cases. There were no rectovaginal fistulae or wound separations. Anal cryptitis developed in one case.

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***Discussion* by CLYDE V. VON DER AHE, M.D., *Los Angeles***

For any operative obstetrical procedure, speaking generally, complications exist. This factor, when properly weighed and evaluated, will determine the safety of any given procedure. The solitary objection to the use of median episiotomy has been the danger of downward extension through the anal sphincter and rectal mucosa. In the series presented by Dr. McNulty, this occurred in only 0.5 per cent. The usual incidence varies from two to four per cent.

As important as it is to know how to properly repair a complete (or incomplete) third degree perineal laceration, I think it is equally important to know the limitations of median episiotomy; so that when it is used we can anticipate that the incidence of third degree perineal laceration will drop, and eventually parallel the incidence following mediolateral episiotomy.

Briefly to review and reemphasize this, the conditions limiting the use of the median episiotomy are listed in the order of their importance:

1. The subpubic arch or the anterior pelvic depth. As the arch becomes more narrowed, the fetal head is forced more posteriorly, in order to gain enough room to pass under the arch.

2. Malposition of the fetal head, particularly persistent occiput positions and deep transverse arrests.

3. The use of forceps. I am happy to hear Dr. McNulty emphasize this point. It has been my conviction for a long time that the shank and the blades of the forceps are as important as the fetal head in the production of third degree lacerations. Median episiotomy is also contraindicated in cases of forceps-rotation, and in breech deliveries with forceps on the after-coming head.

4. Not only is the length of the perineal body important, but also the texture of the perineal tissue. The latter, how-

ever, is unpredictable. This tissue may give way readily when a firm perineum is expected.

In the performance of median episiotomy, it is important to incise the vaginal mucosa upward for a distance of at least five centimeters. This procedure not only prevents tearing upward into the vault, but actually allows the repair of the rectovaginal fascia at a higher level than ordinarily would be possible. This, coupled with postpartum perineal exercises, is an important step forward in the prophylaxis of uterine prolapse.

It is my belief that the routine use of the prophylactic angle suture following median episiotomy is important. This suture, introduced by the late Dr. Norman Williams, consists of a double strand of 00 or 000 catgut, placed about one inch lateral to the lowermost point of the episiotomy. It goes through the perineum, comes out in the vagina below the mucosa, and then outward on the opposite side, through the skin of the perineum one inch lateral to the angle of the episiotomy. This suture is tied loosely enough to admit two fingers into the loop. It is a real aid in preventing the downward extension of the episiotomy. We have had but two cases of complete perineal laceration since using this technique, and in one other case it was necessary to cut the sutures because of pronounced edema of the fetus. The suture was cutting the baby's skin.

Finally, I think that the figures presented in Dr. McNulty's paper tend to substantiate the growing feeling that median episiotomy can be used more frequently without materially menacing the patient or increasing the incidence of third degree perineal laceration.

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## Placement Assistance for Doctors

The American Medical Association recently initiated a new program to acquaint physicians leaving military service with existing medical opportunities, and to assist State Selective Service Medical Advisory Committees in replacing deferred physicians classified as Priority 1 under the "Doctor Draft Law."

This program, inaugurated by the A.M.A. Council on National Emergency Medical Service with the cooperation of the Department of Defense and the Selective Service System, has the enthusiastic endorsement of state medical societies and chairmen of Selective Service Medical Advisory Committees.

The names of physicians to be released from service, and other necessary information, will be supplied to the Council on National Emergency Medical Service by the offices of the three surgeons general. The council will communicate with each of these physicians to determine, in general, his post-service plans, his medical qualifications and specialty, as well as the state in which he prefers to work.

The names of physicians interested in receiving additional information will then be grouped by states and sent to State Selective Service Medical Advisory Committees. While these names are being forwarded primarily as potential replacements for deferred Priority 1 physicians, further action, if any, with respect to them will depend entirely on the wishes and desires of the advisory committees.

This same information will be made available to state medical societies through the Physicians' Placement Service of the A.M.A. Council on Medical Service in accordance with current procedures.

—From the A.M.A. *Secretary's Letter*

# Spontaneous Epistaxis

## Theoretical Consideration of Etiologic Factors and Treatment

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*• In a study of data on 136 hemorrhages in 14 patients with posterior epistaxis it was noted that the incidence of bleeding was higher at some hours of the day than at others. The times of highest incidence were more or less inverse to hours of peak systolic blood pressure in normal subjects, suggesting that bleeding occurs as a result of dislodgement of an embolus at times of vasodilation. If that is true, then it should be possible to control bleeding by giving vasoconstrictive drugs. There are not as yet enough data on trial of that method to warrant conclusions.*

SPONTANEOUS EPISTAXIS is at least annoying to the patient and, if it is severe or recurrent, may be alarming. That there is no uniformly effective means of treatment is indicated by the number of articles in the literature describing various methods.

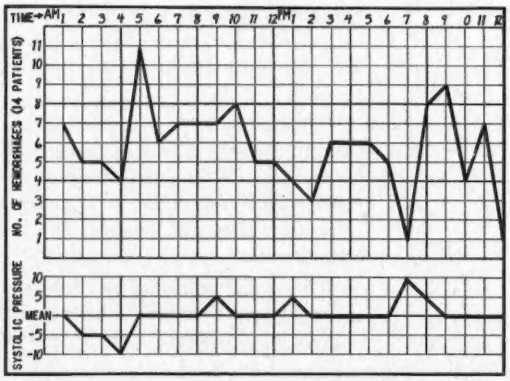
The author, following the example of several other investigators, designates hemorrhage arising anteriorly to the anterior end of the middle turbinate as *anterior* and hemorrhage from a site posterior to that line as *posterior*. Table 1 presents data on the incidence of bleeding from each of these two areas as noted by Hallberg,[1] by Ogura and Senturia,[3] and by the author. The data reported by Hallberg and by Ogura and Senturia indicate the incidence in hospital or clinic practice, and the author's data indicate the incidence in ordinary office practice of rhinology.

Treatment of anterior hemorrhage, mostly from Little's or Kiesselbach's area, is rarely a problem, but control of posterior bleeding may be extremely difficult. Therefore, records of 14 patients who were hospitalized for treatment of spontaneous epistaxis of posterior or unknown origin were reviewed to appraise the method of treatment and to consider factors that may be related to the onset and recurrence of hemorrhage, and possibly to control. The only basis of selection was that the patients were hospitalized and accurate records were available. Epistaxis was most commonly observed in patients in the fifth and seventh decades of life. Data were collected on 136 hemorrhages in the 14 patients.

Nasal packing was used as a measure to control bleeding in all cases, and in many instances postnasal packing also. In two patients the bleeding was from a point far posterior in the inferior meatus and had the characteristics of bleeding from the nasopharyngeal plexus as described by Woodruff.[5] It was controlled by packing the bleeding area under the turbinate and placing a second pack between the turbinate and the septum to keep the former pack in place. In all other cases in which there was more than one hemorrhage during the time in hospital, there was bleeding through the packing. The amount varied from slight oozing to profuse bleeding, despite adequate packing.

The hour of onset of the 136 episodes of bleeding was charted (Chart I) and it was noted that the incidence of onset was low in the four hours after mid-

CHART I




Comparison of time of onset of bleeding in present series with hourly blood pressure variations in normal subjects.[2]

TABLE 1.—*Site of Bleeding in Various Series.*

| | Anterior | Posterior | Undetermined |
|---|---|---|---|
| Hallberg* | 33% | 22.7% | 28.3% |
| Ogura and Senturia | 63% | 37 % | ..... |
| Author | 76% | 18 % | 6 % |

*Percentages total less than 100 because certain hemorrhages caused by other factors were excluded.

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night and highest at 5 a.m. There was a slight rise at 10 a.m. and a decline from then until 2 p.m. The lowest incidence of the day was at 7 p.m. A secondary peak occurred at 9 p.m.

Since frequent observation of the blood pressure of patients in the present series was not practical, data from Mueller and Brown[2] on hourly variations in systolic blood pressure from the mean in 26 normal persons was charted (Chart I) for purposes of comparison with the incidence of bleeding in the 14 patients studied.

The questions that arose from the foregoing observations, and the conclusions drawn, were as follows:

1. Is nasal and/or postnasal packing a successful method of controlling epistaxis?

Where "spot packing"—that is, packing directly over the bleeding vessel—was possible, the method was successful. In all other cases, bleeding persisted despite packing. In the present series, ligation of the external carotid artery was resorted to in three cases after adequate packing, multiple transfusions and other supportive measures had failed. Ligation controlled the bleeding and had no undesirable sequelae. It is the author's conclusion that in many cases packing is not a satisfactory method of control of epistaxis.

2. Is there a cyclic incidence of onset of recurrent bleeding?

The author believes that the data as to hour of incidence (Chart I) indicate that there is.

3. Is the onset of hemorrhage related to blood pressure?

It is to be noted in Chart 1 that the peaks of incidence of hemorrhage do not correspond with peaks of systolic blood pressure. The period of sustained fairly high pressure during the afternoon is not associated with a high incidence of onset of bleeding, and indeed the hour of lowest incidence of bleeding is the same as the hour of highest blood pressure.

4. Is peripheral vasodilation a factor in recurrence of hemorrhage?

One factor which may be of significance in cessation of arterial bleeding is contraction of the stria muscularis which closes or narrows the lumen. Vasodilation, by enlarging the lumen so that the thrombus no longer occludes it, may permit bleeding to recur. Chart I suggests such a possibility: the period of lowest blood pressure, and therefore greatest vasodilation, is followed by the high peak of onset of hemorrhage at 5 a.m. The secondary peak at 9 a.m. follows a period of declining blood pressure.

Assuming that hemorrhage does occur as a result of vasodilation, it should be possible to control it with vasoconstrictive drugs. The successful use of pituitrin to control pulmonary bleeding as reported by Rist in 1911 and more recently by Trimble and Wood[4] and others is based on this principle. Intravenous use of pituitrin causes vasoconstriction almost immediately and the effect lasts about 30 minutes. Other drugs—such as ephedrine, Propadrine® and Neosynephrin®—that have a direct action on smooth muscle of the vessel walls and that are sympathomimetic may be given in coated tablets or capsules timed to produce vasoconstriction at the times when epistaxis is most likely to occur. It is suggested that they be given along with small doses of barbiturates at least twice a day. As the commonly used enteric coating will liberate the drug in about four hours, the drug should be given at about 5 p.m. and again at midnight. The presence of extremely high systolic blood pressure would of course contraindicate the use of such drugs owing to the possible danger of cerebral accident. Epistaxis in such circumstances might be beneficial.

Observations are being made on the effectiveness of this means of therapy, but not enough data to warrant conclusions have been accumulated.

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4. Trimble, H. G., and Wood, J. R.: Pulmonary hemorrhage: its control by the use of intravenous pituitrin, Dis. of Chest, 18:345, Oct. 1950.

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***Discussion by* LELAND G. HUNNICUTT, *Pasadena***

Dr. Hollingsworth apparently has made an accurate observation that bleeding occurs while the blood pressure is low, rather than when it is high as we have always supposed in the past.

An internist with whom I discussed the subject expressed belief that bleeding is liable to occur when the patient gets up in the night to go to the bathroom, as there is a tendency to blow the nose before going back to bed. This is an observation for which I cannot vouch. I would like to suggest another cause—that drying in the posterior part of the nose weakens the mucous membrane overlying the bleeding point. One of the terminal branches of the sphenopalatine artery extends from the sphenopalatine foramen over to the middle turbinate and another down to the inferior turbinate. The artery is nearest the surface at the point at which it enters the posterior and lateral part of the inferior turbinate. There it can be seen in outline under the mucous membrane. The inspired air rushing over this area has a pronounced drying effect. I have noticed that a patient who is extremely restless is less liable to have a nose bleed than one who sleeps soundly.

Dr. Hollingsworth has stimulated our thinking on this most difficult problem, and any new information that can be brought out is of benefit to all of us.

# CASE REPORTS

- **Familial Pseudohypoparathyroidism**
- **Fatal Aplastic Anemia Following Chloramphenicol (Chloromycetin) Therapy**
- **Acute Exfoliative Dermatitis Due to Dormison®**
- **Salmonella Infection in a Premature Infant with Congenital Anomalies**

## Familial Pseudohypoparathyroidism

### *A Report of Two Cases*

HELEN MACKLER, M.D., J. R. FOUTS, M.D., *and* J. W. BIRSNER, M.D., *Bakersfield*

THE FIRST THREE CASES of so-called pseudohypoparathyroidism to be described were reported by Albright and his colleagues in 1942.[1-4, 6, 9-16] Since then 22 additional cases have been reported. One of the authors (H.M.), unacquainted with the possibility that the condition might be familial (Elrick[9]), found five additional probable cases in three generations of the family from which the sister and brother reported upon herein derived. It seems highly probable that many subclinical cases—with subnormal mentality as a manifestation—might be recognized if the relatives of each patient with florid expression of the disease were studied.

Since Albright's published description of a pseudo form of this clinical entity, relatively few instances of "idiopathic hypoparathyroidism," a previously widely recognized clinical entity, have been recorded. Does this suggest that pseudohypoparathyroidism, especially in the incomplete form, may be more common than true instances of hypoparathyroidism?

Prominence of one aspect of the clinical picture may defeat recognition of the syndrome as a whole. In the cases which have come to the attention of the authors, almost all fields of medical practice have had primary interest—general medicine, endocrinology, pediatrics, dermatology, psychiatry, neurology, radiology, pathology, general surgery, orthopedics, urology, ophthalmology, dentistry and human genetics.

In the three cases reported by Albright, the patients had tetany associated with hypocalcemia and hypophosphatemia that was not affected by injection of parathyroid hormone. All the patients had retarded intelligence, a round face and short stature. Epilepsy had been diagnosed initially in one patient. This diagnosis had been made also in cases reported by other investigators.

Stunting of growth, particularly noticeable in the metacarpal and metatarsal bones and in the teeth, and associated with early closure of the epiphyses, appears at an earlier age in pseudohypoparathyroidism than in idiopathic hypoparathyroidism. The metacarpal bones, unlike those observed in Brailsford's[7] syndrome, vary in length. Congenital vascular anomalies, as noted in Turner's syndrome, are not apparent. Females are predominantly affected—an observation common to both pseudohypoparathyroidism and Turner's syndrome.

Pseudohypoparathyroidism is characterized by the following signs and symptoms: short stature; broad face; subnormal intelligence; unerupted teeth; thick skull; thick and short metacarpal and metatarsal bones; convulsive seizures; tetany, active or easily produced; increased centers of ossification; electroencephalographic irregularities; calcifications of the soft tissues, especially intracranial; hypocalcemia; elevated phosphorus content in the serum; low content of phosphorus in the urine; lack of responsiveness to parathyroid hormone (Ellsworth-Howard[8] test) and diminution of other glandular components. Not all these criteria need be present to warrant a diagnosis of pseudohypoparathyroidism. Bakwin[5] reported in 1921 that a high proportion of infants with tetany had broad faces; Browne (cited by Selye[14]) described the mother of a patient as having only portions of the syndrome. One of the patients reported upon by Elrick[9] responded to injection of parathyroid hormone with only moderate increase in urinary phosphorus and decrease in serum phosphorus. Metacarpal stunting was not present in a case reported by Medill.[11] Berardinelli[6] did not submit the patient to testing with hormone in a case reported by him.

The occurrence of the syndrome in siblings was not described until Elrick,[9] in 1950, reported upon pseudohypoparathyroidism in identical twins; he also mentioned similarly involved twins observed by Talbot and Crawford.

Pseudohypoparathyroidism in a sister and a brother is reported herein. When the diagnosis of pseudohypoparathyroidism in one case, that of a 22-year-old woman, was established, the family was requested to bring in the other siblings. A 16-year-old sister and a 10-year-old brother were entirely normal, although of short stature like the mother. (The shortness of stature was considered coincidental.) The fourth child, a boy 29 months of age (Case 2), had unequivocal signs of pseudohypoparathyroidism. Members of three generations of the family have at least some features of the syndrome. The paternal grandmother has thickening of the skull, a tendency to short, thick metacarpal bones, and a greatly increased number of sesamoid bones in the hands and feet. She previously had noted that slow learning together with a broad face seemed to be a family characteristic. Of her 13 children, three had died during convulsions while infants and three of her living children have broad faces. Two of this second generation have been examined. They have thickened skulls and each has at least one

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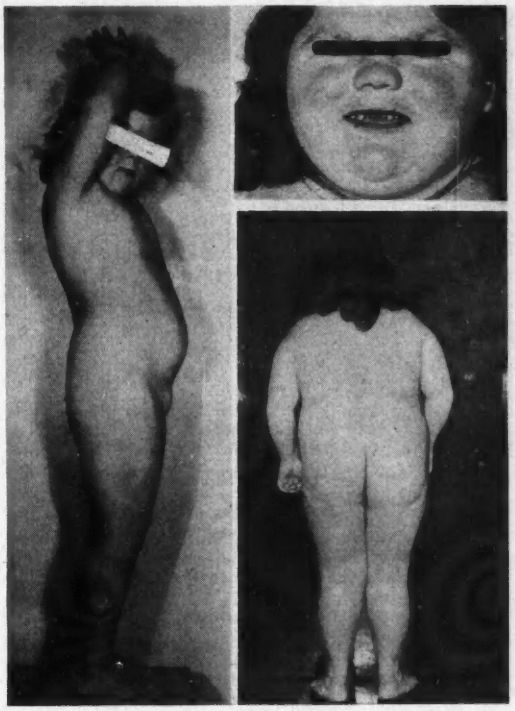


Figure 1.—*Left*, the patient (Case 1) at the age of 9 years. *Right (upper and lower)*, same patient at 22 years of age.

somewhat thickened and shortened metacarpal bone. Another brother, not yet examined, has facies typical of the condition. An apparently normal sister has a round-headed, mentally retarded son.

## REPORTS OF CASES

Case 1: The hospital record of a woman 22 years of age who was admitted to the Kern County General Hospital, Bakersfield, described her as having been "short and squatty," at the age of two years when she was first admitted. No specific diagnoses or tests were recorded at that time.

When she was seven years of age she was readmitted. In the history taken at that time it was noted that a convulsion had occurred at the age of three months and a series of generalized convulsions at the age of five years. The patient was 4 inches shorter and 20 pounds heavier than the average 7-year-old girl. The blood pressure was 130 mm. of mercury systolic, 100 mm. diastolic. The blood and the urine were normal except for traces of albumin in the urine. A glucose tolerance test recorded a flat curve with a maximum of 190 mg. per 100 cc. of blood a half hour after injection and a decrease to 60 mg. at the end of six hours. The urine was sugar-free during the test. Roentgenographically, the skull was considerably thickened; there was widening of the right fifth metacarpal bone and lipping of the distal ends of the fifth metatarsal bones.

At the age of eight the patient had several convulsive seizures characterized by hyperventilation followed by opisthotonos and a short period of deep sleep.

When the patient was nine years of age her stature was still retarded (Figure 1) and she was grossly overweight. In roentgenograms taken at that time the fifth metacarpal bones were observed to be short, wide and curved, with areas

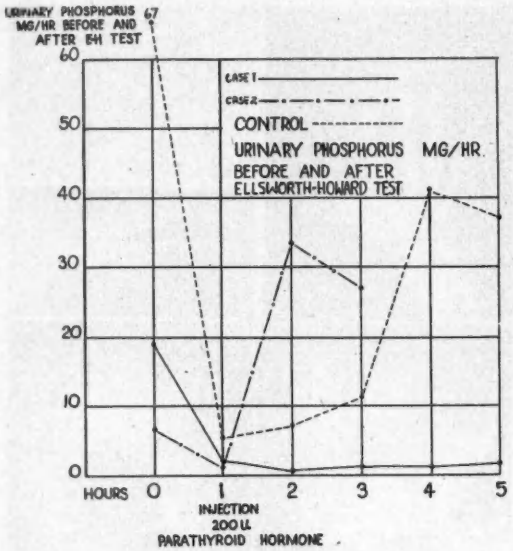
Figure 2.—Photograph of hands and x-ray films of metacarpal and metatarsal bones and skull taken when patient (Case 1) was 22 years of age.

of decalcification in the central portion of the diaphyseal ends; and the bones of the skull were greatly thickened throughout. The calcium content in the serum was 8.6 mg. per 100 cc. on one occasion and 7.9 mg. a few weeks later. The basal metabolic rate was approximately minus 3 per cent.

The patient was not observed again until the time of readmittance at 22 years of age. She had received no definitive therapy in the interim. Her height was 53 inches and her weight 149 pounds. Her "mental age" was about six years and she was pleasant and cooperative. She had had three menstrual periods at approximately the age of 15, but none since. Convulsions had not occurred for several years. The voice was coarse and hoarse, the skin of the face florid. Trousseau's sign was readily elicited and was not altered in appearance or disappearance by hyperventilation. There were no defects in vision. Visible calcifications of the soft tissue were not noted. Great thickening of the calvarium, calcification of the basal ganglia and many unerupted teeth were observed roentgenographically. The patient had only 12 erupted teeth, most of them notched. The metacarpal and metatarsal bones were characteristically shortened, with bowing of the radii (see Figure 2).

An Ellsworth-Howard test was done (see chart). Injection of 200 units of parathyroid extract demonstrated inability to mobilize phosphorus in the urine; there was no concomitant change in the phosphorus content in the serum.

The patient was given a high protein diet relatively low in phosphorus with 1 gm. of calcium gluconate per day and approximately 150,000 units of vitamin D per week. After six months of this regimen, the body weight was 30 pounds lower and the complexion no longer florid. The patient had progressed three grades in reading. Subcutaneous areas of calcification had appeared and were expanding. The calcium content of the serum rose from 6.5 mg. to 7.88 mg. per 100 cc., and the phosphorus content decreased from 5.5 mg. to 4.7 mg. per 100 cc. The urine was usually nearly free of calcium by Sulkowitch's test.




CASE 2: A brother of the patient in Case 1 was first observed at the age of three weeks with complaint of cyanosis during what was described as a "chest cold." The patient had fever, cough and intermittent cyanosis. There were many rales in the chest. He promptly became cyanotic when laid flat, although the color became satisfactory when he was held upright. Upon roentgenologic examination it was noted that the thymus was not enlarged and there appeared to be no obstruction of the trachea. Cyanosis disappeared with the clearing of the pneumonitis.

When the patient, whose parents considered him well and normal in development, was admitted to the hospital for examination at the age of 29 months, the general skeletal configuration that has been noted in other cases of pseudohypoparathyroidism was observed. Chvostek's sign was present. The child was not yet talking and was still nursing. In roentgenograms the calvarium was observed to be nearly twice as thick as normal, and the fifth metacarpal bones were thick, dense and shortened. Dental development was subnormal, only 16 teeth having erupted (see Figure 3). There was a small subcutaneous calcification over one ankle, but no calcification in the basal ganglia. Intravenous administration of 200 units of parathyroid extract slightly increased the content of phosphorus in the urine although the amounts appearing in the urine were considerably less than those of the control, an adult who was given 100 units of the same preparation.

The same regimen that had been followed by the patient's sister was prescribed, except that the amount of vitamin D was 100,000 units per week. The calcium gluconate solution replaced milk. The patient's speech improved rapidly and he became more alert. Subcutaneous calcification over the ankle increased steadily in size.

## SUMMARY

Pseudohypoparathyroidism in a 22-year-old woman and in her 29-month-old brother is reported. Some of the characteristics of the syndrome were noted also in the paternal grandmother, in at least three of her thirteen children, and in one other grandchild in addition to those reported upon. Previously reported cases of pseudohypoparathyroidism are cited and the characteristic features of the syndrome are described briefly.

518 Haberfelde Building, Bakersfield (Mackler).

Figure 3.—Patient in Case 2.

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# Fatal Aplastic Anemia Following Chloramphenicol (Chloromycetin) Therapy

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CHLORAMPHENICOL (Chloromycetin®) was first produced in 1947 from the soil actinomycete[5] and has been shown to be effective clinically against many organisms pathogenic in humans. Ease of administration, availability, moderate cost and the low incidence of gastrointestinal irritation associated with it have contributed to widespread use of the drug. These would be favorable attributes of any therapeutic agent, yet they could be nullified to a great extent if the agent in question had a considerable degree of toxicity, even though injury from it occurred infrequently.

Following is a report of a case of fatal aplastic anemia that developed after six weeks of therapy with chloramphenicol.

## CASE REPORT

A 35-year-old white married woman was admitted to the French Hospital on March 7, 1952, because of generalized icterus, anorexia and lassitude. The illness had begun Jan. 10, 1952, with fever, chills and symptoms of irritation of the bladder. These symptoms were intermittent for the next ten days, and the patient was examined in the urological department of the hospital on January 23. A specimen of urine obtained by catheter had specific gravity of 1.005 and contained a trace of albumin. There were 5 erythrocytes per high power field, occasional leukocytes and epithelial cells. A culture was negative for acid-fast bacilli, but on it grew organisms morphologically and biochemically resembling Pseudomonas aeruginosa.

The patient received one injection of 400,000 units of procaine penicillin on January 23 and chloramphenicol, 250 mg. thrice daily, was prescribed. An intravenous urogram and x-ray of the chest on Jan. 24 were reported as within normal limits. When observed Jan. 30 and Feb. 6 the patient said she felt a great deal better. A nine-hour sample of urine was examined by Addis' method on Feb. 1, 1952. The following was reported: Total quantity 850 cc., specific gravity 1.005, acid reaction, albumin quantitative 1.7 gm., erythrocytes 136,666, casts 700, and leukocytes 666.

On Feb. 22 chills, fever and sweating developed, lasted one day, and were followed by malaise, anorexia, nausea and weakness. Jaundice was first noted by the patient on March 1. It increased gradually until admittance to hospital on March 7.

In the six weeks preceding admittance to the hospital the patient had taken a total of approximately 30 gm. of chloramphenicol and no other medication.

*Past History.* Chronic glomerular nephritis had existed since 1947, apparently a result of streptococcal infection of the throat in 1946. The patient had been rather closely observed in the interim, during which she carried out the duties of a housewife and mother in a normal manner, and objective studies from time to time indicated very little progression of renal disease. Specimens of urine were constantly of low specific gravity. Mild proteinuria was present, and occasionally hematuria was noted microscopically. Intravenous urograms were normal except for somewhat faint concentration of dye. Hemograms were within normal limits. The blood pressure varied from 130 mm. of mercury systolic and 96 mm. diastolic to 150 mm. and 104 mm. respectively. In December 1950 the urea nitrogen content of the blood was 15 mg. per 100 cc. In December 1950 abortion was done as a precautionary measure in view of the renal disease.

From the Department of Medicine, French Hospital, San Francisco.

Upon physical examination March 7, 1952, the patient was observed to be well developed and well nourished. She was not in acute distress, but pronounced jaundice was present. The edge of the liver was palpable two fingers' breadth below the right costal margin and it was slightly tender on percussion and deep palpation. Temperature, pulse and respirations were normal. The blood pressure was 140 mm. of mercury systolic and 90 mm. diastolic. Erythrocytes numbered 4,070,000 per cu. mm. and the hemoglobin content was 12.4 gm. per 100 cc. Leukocytes numbered 6,100—68 per cent neutrophils and 32 per cent lymphocytes. Platelets were reported as normal. Urinalysis showed specific gravity of 1.003, a trace of albumin, no sugar, one plus bile, two to four leukocytes per high dry field, and many epithelial cells.

Prothrombin time was 82 per cent of normal. The icteric index was 115 units, thymol turbidity 28 units, urinary urobilinogen 1.26 Ehrlich units, serum cholesterol content 210 mg. per 100 cc., total protein content in the serum 8.6 gm. per 100 cc. (albumin 3.3 gm. and globulin 5.3 gm.), serum bilirubin content 14.3 mg. per 100 cc. (direct reaction 2.3 mg. per 100 cc.) Cephalin flocculation was two plus.

A diagnosis of viral hepatitis was made. The patient was kept in bed and a diet high in protein, carbohydrate and vitamins was prescribed. Thiamine chloride, 10 mg. daily, was given and there was no other medication. The patient made excellent progress and on March 21 the icteric index was 22 units, thymol turbidity 9.5 units, and the urine negative for bile.

On the same day, the patient noted a few petechiae on her arms and attributed them to scratching. Next day the number of petechiae had increased, but the patient said she felt well. On this day bleeding time was 1½ minutes and clotting time 7 minutes. The following evening, March 23, catamenia began and became profuse. A persistent cough productive of a bloody sputum developed and there were increasing numbers of petechiae and areas of ecchymosis over the entire body. Erythrocytes numbered 1,450,000 and the hemoglobin content was 4.6 gm. per 100 cc. of blood. The cell volume was 14 per cent of the whole blood. Leukocytes numbered 3,200—51 per cent neutrophils and 48 per cent lymphocytes. No platelets were observed in the blood. Bleeding time was 5 minutes, clotting time 12 minutes, and there was no clot retraction in 8 hours. Urinalysis showed three plus albumin, no sugar, 40 to 50 erythrocytes per high dry field and specific gravity of 1.010. Erythrocyte fragility was normal and the result of Coombs' test was negative. The sternal marrow was hypoplastic and no megakaryocytes were noted in it. No marrow substance could be aspirated from the spinous process in two attempts.

Following are data on results of examination of the blood at various times during the last period of hospitalization:

| Date 1952 | Hemoglobin gm. per 100 cc. | Erythrocytes (Per cubic millimeter) | Leukocytes (Per cubic millimeter) | Platelets (Per cubic millimeter) | Leukocyte differential (per cent) Neutrophils | Lymphocytes | Eosinophils |
|---|---|---|---|---|---|---|---|
| Mar. 7 | 12.4 | 4,070,000 | 6,100 | Normal | 68 | 32 | |
| Mar. 24 | 4.6 | 1,450,000 | 3,200 | None seen | 51 | 48 | 1 |
| Mar. 25 | 9.2 | 3,160,000 | 2,200 | None seen | 43 | 53 | 4 |
| Mar. 26 | 12. | 3,960,000 | 1,100 | 11,000 | 41 | 59 | |
| Mar. 28 | 11. | 3,640,000 | 1,200 | Too few for accurate count | 28 | 71 | 1 |

Six 500 cc. transfusions of whole blood, including 1,500 cc. of fresh whole blood, were given between March 24 and March 26, but the condition of the patient deteriorated rapidly. The pulse rate rose to 120 per minute. Respirations were shallow and labored and the rate 40 per minute. The rectal temperature reached 103° F. New showers of petechiae appeared daily, and gross melena, epistaxis, gingival bleeding, hemoptysis and vaginal bleeding continued. The patient became progressively weaker and died March 29.

In addition to blood transfusions and general supportive measures, the patient was given penicillin, 600,000 units daily, corticotropin (ACTH), caffeine sodium benzoate, and oxygen both by mask and positive pressure.

## NECROPSY

The skin of the entire body was faintly icteric, and over the skin of the trunk, the extremities and the abdomen were multiple purpuric areas 3 mm. to 10 mm. in diameter. Multiple purpuric areas were present over the surface of the diaphragm, along the wall of the stomach and on the mucosal and serosal surfaces of the small bowel. Semi-liquid, black tarry fecal matter was present in moderate amount in the terminal ileum and in progressively greater quantity distally to the colon. No evidence of ulcer or neoplasm was noted in the gastrointestinal tract, which was patent throughout.

Sections of bone marrow from the sternum and vertebrae were essentially similar histologically. Fat cells were predominant with sparsely scattered clusters of myeloid elements lying between. The distribution was not uniform, some areas approaching a normal degree of cellularity and other areas being entirely adipose. In most regions there were at least a few marrow elements between the fat cells. There were representatives of all constituents present, but the lymphocytic series was more prominent. Megakaryocytes were rare.

The heart weighed 275 gm. The external surface of the pericardium was smooth and the pericardial cavity contained a small amount of straw-colored fluid. The cardiac chambers, endocardial surface, valve leaflets and coronary vessels showed no abnormalities. Microscopically the cardiac muscle fibers appeared of normal size and shape with no evidence of infiltration or scarring of the myocardial tissue.

The left lung weighed 575 gm., the right 975 gm. Both pleural cavities contained minimal amounts of straw-colored fluid. The mucosa of the bronchi was deep pink and copious amounts of fluent blood were present in the lumen. The parenchyma of the lungs was deeply mottled, with a deep, shiny, blackish purple the predominant color. Only near the apices were there small areas resembling normal lung tissue. Both lungs were hypocrepitant and had a solid hepatic feeling on palpation. Cut sections revealed approximately 80 per cent of the lung mass to have a deep purple, solid appearance, with small purple, jelly-like clots emerging from the surface. On microscopic examination the normal architecture of the pulmonary tissue was almost entirely obscured. In some areas massive amounts of red cells and a pink-staining, homogenous material filled the alveoli and some segments appeared entirely airless. No evidence of tumor was noted.

The spleen weighed 125 gm. The capsule was smooth and of uniform slate-gray color. On section the surface appeared uniformly firm, and malpighian corpuscles were evenly distributed throughout the parenchyma. Microscopically the architecture of the spleen appeared to be within normal limits.

The liver weighed 1,500 gm. The external surface was smooth and glistening. The margins were sharp and well defined. Sections were a normal reddish-brown, and lobular markings were clearly visible. A normal lobular pattern was present, with slight thickening of the portal triads, but no extension of these structures. The thickening was due chiefly to lymphocytic infiltration involving about one-half of the triads. Slight fibroblastic proliferation was noted. The most striking feature was disarray of lobules in many areas. The liver cords, particularly at the lobular centers, were obscured and the liver cells haphazard in disposition. They were variable in size and shape with occasional multinuclear forms. Also noted at the lobular centers, quite commonly, were dilated canaliculae containing bile thrombi. These were seen in every second or third lobule. The sinusoids were not distended. The Kupffer cells were enlarged, and many contained brown granular pigment, apparently hemosiderin.

The gallbladder was a turgid, deeply mottled, dark purple sac. It contained a quantity of purplish, jelly-like clots and

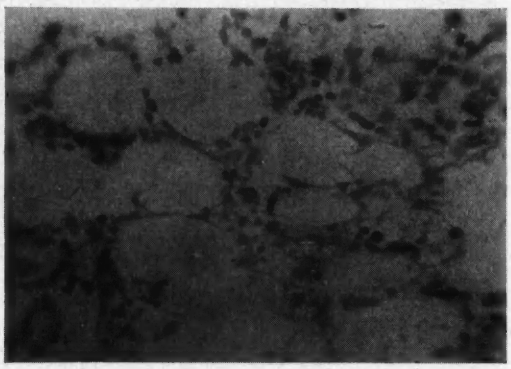

Figure 1.—Bone marrow (high power) showing acellularity.

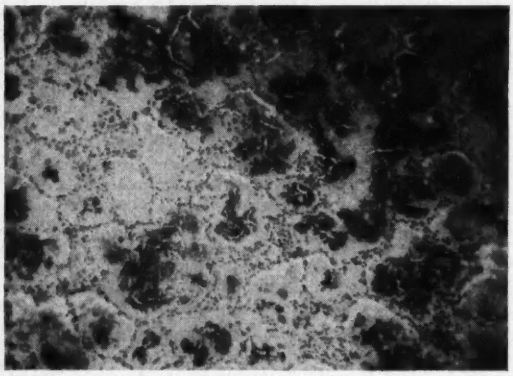

Figure 2.—Lung (low power). Note hemorrhage into alveoli.

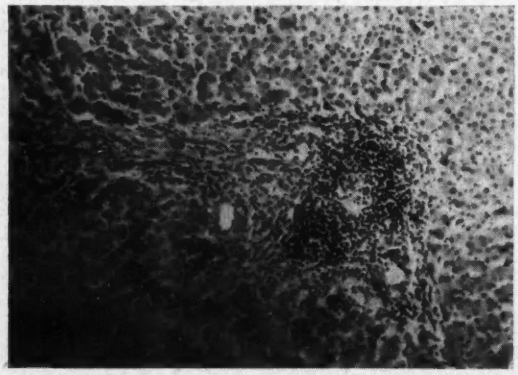

Figure 3.—Liver (high power). Note periportal round cell infiltration.

viscid purplish-black mixture of blood and bile. There were large amounts of blood within the fibers of the muscular coat and infiltrating into the mucosal layer. No stones or tumors were present in the gallbladder or common duct.

The adrenal glands were grossly normal. Microscopically the usual pattern of the glands did not appear to be disturbed.

Each kidney weighed 118 gm. The capsules were stripped with ease, revealing finely pebbled or granular surfaces, which were diffusely covered with small dark purpuric nodules approximately 1 mm. or less in diameter. Many of the glomeruli had undergone partial or complete hyalinization. Those which were not involved were enlarged and excessively cellular. Occasional remnants of crescents were noted and there was capsular adhesion at many points. The convoluted tubules were disposed in clusters of dilated elements separated by areas of lymphocytic infiltration and fibrosis in which the tubules were greatly diminished. The dilated lumina contained hyalin and acidophilic casts. The glomerular capillaries were narrowed where hyalinization had not supervened. Symmetrical thickening of the walls of the smaller divisions of the arterial tree was noted, whereas the larger divisions were relatively free of sclerotic change. There was little inflammatory infiltration in the medulla and the pelvic membranes were uninvolved.

The final diagnosis was: 1. Marked hypoplasia of the bone marrow; 2. Chronic glomerulonephritis; 3. Subacute hepatitis; 4. Massive tissue hemorrhage into lung parenchyma, bilateral.

## DISCUSSION

It seems clearly established that aplastic anemia with the typical clinical manifestations and changes in the bone marrow and peripheral blood may be produced by a variety of toxic substances.[19] This so-called secondary aplastic anemia differs in no way clinically or histologically from the idiopathic form, which by many observers is regarded as also caused by irreversible chemical injury from an unrecognized source[21] or possibly actually representing the marrow of aleukemic leukemia. It is sometimes difficult to prove conclusively that an etiological relationship exists between the disease state and the potentially toxic substance to which the person is exposed.

In some instances, as is the case in the etiological relationship of benzol and its derivatives, arsphenamine, irradiation, trinitrotoluene, and a few others, the evidence is so overwhelming as to be conclusive.[19] There are varying degrees of susceptibility. Some persons react violently, others slightly or not at all. A native idiosyncrasy to a drug may exist or sensitization may develop after long exposure or repeated short exposures. The concentration or the total amount of the suspected agent may be an important factor in the development of the adverse reaction.

Any substance which contains the nitrobenzene radical should be regarded with suspicion;[3] and Smadel[16] pointed out the presence of this radical in the structure of chloramphenicol and warned of its possible toxic effect on the hematopoietic system.

In attempting to evaluate the role played by any suspected therapeutic agent in the production of toxic effects, it is necessary to consider the possible etiological relationship of the disease state being treated as well as the effects of other drugs being administered. The patient here reported upon was known to have had chronic glomerular nephritis for the preceding five years, but there was very little evidence clinically of progression of the renal disease. It is well known that anemia is a fairly common complication late in nephritis, more commonly with the advent of uremia. The exact mechanism is not clear, but a depressant effect on the hematopoietic system by retained toxic metabolites is considered most likely.[1] However, the development of an acute fulminating episode on the basis of preexisting renal impairment of the degree described would indeed be exceedingly unusual.

Another factor which must be evaluated in the present case is the hepatitis which developed approximately four weeks after treatment with chloramphenicol was begun. The list of chemical substances capable of causing liver damage is quite extensive, and among the aromatic compounds, nitrobenzene has been shown to possess this property. Clinically, the manifestations of hepatitis are the same whether the etiological factor be toxic or viral. Differentiation depends on the history and histological studies. Lichtman[10] stated that in non-fatal viral hepatitis the lesions are generally zonal in distribution and cell necrosis extremely rapid. Cellular reaction is non-leukocytic and periportal cellular infiltrates consist primarily of round cells and eosinophils. In toxic hepatitis, cellular necrosis is gradual; that is, more coagulative. The usual pattern of destruction is not zonal, because the poisonous agent attacks the entire lobule with equal severity, producing all stages of cellular disintegration. In regions which remain intact, the inflammatory reaction consists largely of neutrophils. Lepper and co-workers[9] produced histologic changes in the livers of mice and dogs by administering large doses of aureomycin, of terramycin and of chloramphenicol. Rich and co-workers,[14] in a report of a fatal case of aplastic anemia following chloramphenicol therapy, described scattered foci of liver necrosis noted at necropsy. As jaundice had not developed, they regarded the necrosis as a late event and they stated that foci of hepatic necrosis develop in some cases of marrow aplasia regardless of cause.

In a search of the recent literature no report of an instance of toxic hepatitis resulting from the therapeutic administration of chloramphenicol was found, and it seems quite likely that the patient in the present case had infectious hepatitis; both the clinical course and the histologic changes in the liver were entirely consistent with that condition—in fact were more suggestive of it than of primary toxic disease.

The possibility that hepatitis induced the bone marrow aplasia seems exceedingly remote, especially in view of the clinical course and histological observations. Post, Gellis and Lindenauer[12] in studies of the sequelae of acute infectious hepatitis in 114 patients made no mention of aplastic anemia.

In reviewing factors that might have caused the changes in the bone marrow, then, consideration must be given to chloramphenicol. It has been shown by repeated animal experiments that the subcutaneous injection of benzene will produce a depression of the bone marrow and concomitant reduction of the leukocytes in the blood to 200 or 300 per cu. mm., with complete absence of granulocytes.[8] Dietz and Steinberg[4] in a report on a study of the chemical composition of rabbit bone marrow in benzene poisoning stated the action of benzene on the marrow was to increase its water content and to decrease the amount of lipid, total and non-protein nitrogen and non-protein sulfur fraction.

In the past two years there have not been a great many reported instances of bone marrow depression following the use of chloramphenicol, but they seem to be on the increase. Volini and co-workers[20] reported the development of bone marrow hypoplasia in three patients treated with chloramphenicol for periods of nine to nineteen days during which the total amounts given were 26 to 53 grams. Granulocytopenia developed in all, with involvement of the erythrocyte element in one. All responded favorably when use of the drug was discontinued. Gill[6] reported the development

of granulocytopenia in two infants treated with the drug. One of them received approximately 6 grams in 12 days and the other 2 grams in 2 days. Both recovered when use of the drug was stopped. Rich and co-workers[14] reported a case in which fatal aplastic anemia developed in a 63-year-old male who received 57 grams of chloramphenicol over a period of three months for a chronic urinary tract infection. Loyd[11] reported a case of fatal aplastic anemia following treatment with chloramphenicol intermittently over a period of one and one-half years for a urological disorder. The amount of the drug given was not stated. Two cases of aplastic anemia (one resulting in death) following prolonged use of chloramphenicol were reported by Wilson and co-workers.[22] Both patients received 2 grams weekly (one for 28 weeks and the other for 26 weeks) in treatment for chronic bronchopulmonary suppuration. Patterson[12] reported a case in which severe anaphylactic shock, which required heroic measures to overcome, developed a half hour after 500 mg. of chloramphenicol was administered.

In light of the clinical events, hematopoietic changes and necropsy findings in the present case and in the reports of other observers, the preponderance of evidence appears to incriminate chloramphenicol as a potentially noxious agent capable of inducing severe myeloid depression. In considering associated factors influencing the development of hematologic changes by this agent, length of administration and total dosage must be evaluated.

In the present case the patient received approximately 30 grams over a six-week period—less of the drug and in a shorter period than in any of the other three reported fatal cases. Certainly, thousands of patients have received larger amounts and for greater lengths of time without toxic effect. Gray[7] estimated the incidence of blood dyscrasia concomitant with chloramphenicol therapy at 1 in 400,000. It is worthy of note that in three of the four fatal cases the patients were taking chloramphenicol for a urological disorder. Does impaired renal function play a role in the production of toxic effects by the drug? One must consider the possibility that associated pathologic conditions complicate the disease for which chloramphenicol therapy is given. Possibly patients with impaired renal or hepatic function should not take the drug unless the hematologic effect can be very closely observed. Length of administration may be an important factor, but it would seem from the evidence in the present case that individual idiosyncrasy, or at least hypersensitivity, plays a more vital role.

Other observers[14, 20, 11, 22] have suggested frequent examinations of the blood during therapy with chloramphenicol and discontinuance of the drug at the first sign of depression in granulocytes, erythrocytes or thrombocytes.

In the case here reported the hemogram was normal when the patient entered the hospital and no chloramphenicol was given from that time on. At least in this instance frequent examination of the blood during therapy with the drug would seemingly have furnished little or no warning of impending events. It is regrettable that there was no examination of the blood between the time of admittance and the appearance of purpuric manifestations, two weeks after cessation of therapy with chloramphenicol. However, at that time the patient seemed to be making uneventful recovery from hepatitis and there was no suspicion of toxic effects from previous therapy.

From the standpoint of preventing or modifying the toxicity of benzene and nitrobenzene compounds, Shils and Goldwater[15] conducted some interesting animal experiments. They conclude that, from a practical nutritional point of view, special emphasis should be placed on eating well-balanced meals containing a good proportion of high quality protein and they expressed belief it is probably wise to keep the fat intake at moderately low levels.

It would certainly seem unwise to condemn a drug which has proven its effectiveness against a large group of infections, some of which entail a high degree of morbidity and mortality, merely because of the occasional occurrence of untoward effects. Many lives have been saved and much suffering and loss of time have been eliminated by the judicious use of some of the newer drugs in treating disease states, for which there had been previously no specific or effective therapy. If occasionally in such an instance, despite the observance of all known precautions, an untoward effect results from the therapy, it is regrettable but excusable.

## ADDENDUM

Since this report was prepared there have appeared in the literature three papers with the accounts of eight additional deaths from aplastic anemia following therapy with chloramphenicol.[2, 17, 18] From the increasing number of reports of bone marrow depression associated with the use of this product, it seems mandatory that a definite stand be taken with regard to its employment in the future.

In the author's opinion, it should be prescribed only in those situations where the life of the patient is threatened and where no other type of therapy, with a less toxic potential, has proven to be effective. If all physicians using it are aware of its possible deleterious action, if self-medication by patients is prohibited, and if the blood is continuously scrutinized during use of the drug and for several weeks after it is discontinued, many of the dire results might be avoided.

## SUMMARY

A fatal case of aplastic anemia following chloramphenicol therapy is reported, together with necropsy findings. The possible etiologic relationship of a preexisting chronic glomerular nephritis and coexistent hepatitis is discussed. Closer observation of the hematopoietic system during use of the drug is suggested.

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## ACKNOWLEDGEMENT

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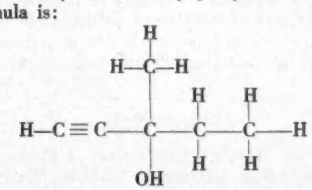
## Acute Exfoliative Dermatitis Due to Dormison®

JAMES N. DeLAMATER, M.D., *Pasadena*

ALTHOUGH even good drugs have dangers and limitations, especially hypnotics which are in great popular demand, considerably more was written about Dormison® in the lay press for the general public than was available to physicians in medical literature when the drug was introduced for sale. In an exhaustive search of recent medical literature only two articles specifically relating to this drug were found, while between October and Christmas 1951, a rash of popular articles appeared in such magazines as the *Woman's Home Companion, Cosmopolitan, Collier's* and *Reader's Digest.*

Tertiary carbinols have long been known to produce central nervous system depression.[1] Margolin and co-workers[2] found that simple unsaturated aliphatic carbinols possessed a high degree of activity, satisfactory duration of action, and low toxicity. Methyl parafynol (Dormison) was considered one of the most promising of these unsaturated carbinols. Chemically it is 3-methyl-pentyne-ol-3 and its structural formula is:



This compound is of considerable pharmacologic interest because the fate of the ethinyl group in body metabolism remains unknown. Inactivation of the drug depends upon destruction of this group.[3]

3-methyl-pentyne-ol-3 has a high selectivity of action. It is not analgesic. It is not anesthetic when administered intravenously in sublethal amounts. It does not appear to be antispasmodic. In contrast to the barbiturates and other hypnotics, even in large doses it does not depress respiration. Caffeine given parenterally causes rapid recovery from the deep hypnotic state caused by the drug and no undesirable after-effects have been observed in animals given overdoses of the drug. 3-methyl-pentyne-ol-3 was tested for chronic toxicity in rats and dogs with daily doses of 200 to 300 mg. per kilogram of body weight (approximately 70 times the recommended human dose). The amount of sugar in the blood, hemoglobin, the number of erythrocytes and leukocytes, and the leukocyte differential remained normal. Dogs had normal renal function when tested for phenolsulfonphthalein excretion.

Dormison is rapidly inactivated in the body. The content of the drug in the blood decreases rapidly although only small amounts are excreted in the urine. The drug is most rapidly inactivated by hepatic and renal tissue. Evanescence of the activity is associated with enzymatic modification of the ethinyl group.[2]

In a clinical study of 134 patients,[2] 3-methyl-pentyne-ol-3 was found to be an effective hypnotic without toxic effects, and free from undesirable side actions. The effective oral dose is 200 to 300 mg. No residual effect was reported on awakening. Some patients, given the drug for over six months, had no untoward symptoms. Before and after the drug was given, studies to determine the cell content of the blood and the amounts of urea nitrogen, creatinine, total serum protein, albumin, globulin, phosphorus, alkaline phosphatase, and cholesterol (free and combined) were carried out. The icteric index was observed and van den Bergh, thymol turbidity or cephalin flocculation tests were done. The urine also was examined before and after medication. No changes attributable to the drug were observed.

The following case appears to be the first reported of toxic reaction to Dormison.

### CASE REPORT

The patient, a Caucasian woman 43 years of age, had redness and blistering of the skin, with a severe burning sensation, and pain in the joints. The condition had existed for three days.

On December 13, 1951, the patient, having read about Dormison in a popular magazine, obtained several capsules of it and that night took two of them for sleep. The next day mild transient itching and red spots on the skin developed. Again she took two capsules that night. The itching and redness were more severe the following day; but still she did not associate the condition with the drug, and at bedtime, because the itching and discomfort were intense,

Presented before the Section on Allergy at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

she took three Dormison capsules for sleep. Next morning she was covered "all over" with a rash that "made her look like a boiled lobster," and numerous large thin-walled blisters had appeared over the face, arms, hands, chest, abdomen, buttocks, thighs and lower legs. The lips and tongue became swollen and there was pain in the wrists, elbows and knees. The patient called a physician, who hospitalized her immediately. She had taken no other drugs in more than sixty days.

Following are the abnormalities noted in a thorough physical examination. The skin over the entire body and face was intensely inflamed and thickened. There were numerous thin-walled bullae 2 to 3 cm. in diameter over the forearms, elbows, axilla, chest, buttocks, thighs and lower legs, as well as denuded areas where the bullae had ruptured and the superficial layers of skin had rubbed off. The scalp was red and swollen with an orange-peel appearance about the follicles. The eyelids were edematous and nearly closed and there was a small bulla on the left upper lid. On the tongue, which was swollen, were teeth markings. The lips were puffed, and inside the left cheek was a 2 x 4 mm. area of erosion. The right breast had been removed. Thickening of the uterine adnexae was noted but there were no palpable masses and no tenderness. Pain was present in the right knee but there was no evidence of accumulation of fluid.

The blood pressure was 120 mm. of mercury systolic and 80 mm. diastolic, the pulse rate 100 and respirations 20 per minute.

Laboratory data were as follows:

| | *Dec. 17* | *Dec. 20* | *Dec. 23* | *Dec. 30* |
|---|---|---|---|---|
| **BLOOD EXAMINATION** | | | | |
| Hemoglobin (gm. per 100 cc.) | 11.6 | 11.5 | 11.6 | 12.0 |
| Erythrocytes per cu. mm. | 4,060,000 | 4,030,000 | 4,050,000 | 4,380,000 |
| Leukocytes per cu. mm. | 5,050 | 6,200 | 6,400 | 6,700 |
| Neutrophils | 83% | 75% | 76% | 73% |
| Immature | 3 | 1 | 1 | 0 |
| Stab | 44 | 13 | 12 | 4 |
| Segmented | 36 | 61 | 63 | 69 |
| Lymphocytes | 12 | 13 | 15 | 22 |
| Monocytes | 3 | 10 | 7 | 5 |
| Eosinophils | 2 | 2 | 2 | 0 |
| Platelets per cu. mm. | 94,000 | 104,000 | ..... | ..... |
| Sedimentation rate (mm. in 1 hour) | 8 | ..... | 10 | ..... |
| Bleeding time | 3 min. | ..... | ..... | ..... |
| Clotting time | 3 min. | ..... | ..... | ..... |
| **URINALYSIS** | | | | |
| Albumin | Trace | 0 | 0 | 0 |
| Sugar (gm. per 100 cc.) | 0 | 2.25 | 0 | 0 |
| Acetone | + | 0 | 0 | 0 |
| Diacetic acid | 0 | 0 | 0 | 0 |
| Microscopic (high power field): | | | | |
| Leukocytes | 15 | 4-5 | 2-4 | 2-3 |
| Erythrocytes | 10-15 | 0-1 | rare | rare |
| Casts | 0 | 0 | 0 | 0 |
| Orthotolidine occult blood | 3+ | Trace | 0 | 0 |

The diagnosis was dermatitis medicamentosa; Dormison sensitivity.

The patient was given 3 ounces of Fleet's phosphosoda at the time of admittance. Thereafter fluids were given intravenously. Corticotropin (ACTH), 25 mg. every six hours, was administered. A diet high in protein was prescribed and vitamins A and C were given in large doses. Penicillin in doses of 600,000 units daily was given prophylactically. As the denuded areas of the skin caused intense discomfort, the patient was given starch baths three or four times daily, and a starch bed into which pounds of dry sterilized corn starch was dusted daily was used.

It was hoped, at first, that the use of sedatives and analgesics could be avoided, for it was not known whether these compounds would exacerbate the condition. Demerol® finally was used in 100 mg. doses, however, without ill effect.

For two days following hospitalization the patient's condition became worse; more bullae formed and larger areas became denuded. On the third day, however, there was pronounced reduction in erythema and swelling, and bullae had stopped forming.

At 3 a.m. of the fourth hospital day, an acute psychotic episode developed, involving olfactory, auditory, and visual hallucinations. This was ascribed to the corticotropin therapy, and use of the drug was discontinued immediately.

Recovery thenceforward was rapid and uneventful and the patient was discharged from the hospital December 27 with a few small residual healing areas. By January 5, 1952, the skin was completely clear.


### SUMMARY

A case of acute exfoliative dermatitis medicamentosa is reported in which the inciting agent appears to have been Dormison (methyl parafynol), the only drug the patient had taken for over sixty days preceding the illness. The disease followed ingestion of seven standard 250 mg. capsules of the drug.



127 North Madison Avenue.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## Salmonella Infection in a Premature Infant With Congenital Anomalies


**JOHN EMMETT, M.D., and JOHN M. CHAPMAN, M.D., Los Angeles**


SALMONELLA TYPHIMURIUM, frequently the etiologic agent in cases of infectious diarrhea in adults and children, rarely is found in newborn infants.[1,2,3]

In the case reported here, S. typhimurium was isolated from a premature infant on the sixteenth day of life. Epidemiologic investigation revealed the probable source of infection. Complete atresia of the duodenum in this case is of added interest because of its possible role in delaying manifestations of infection and prolonging the period of incubation.

### CASE REPORT

An infant who weighed four pounds at birth was admitted to the premature nursery of the Los Angeles County Hospital on the fifth day of life because of vomiting and refusal of feedings. Upon roentgen examination the stomach was observed to be distended with gas. Duodenal obstruction was diagnosed. Laparotomy was done on the sixth day of life and complete atresia of the duodenum above the ampulla of Vater and malrotation of the large intestine was noted. Duodenojejunostomy was performed.

The postoperative course was satisfactory until the eleventh postoperative day, the sixteenth day of life, when severe diarrhea was evident. Salmonella typhimurium grew


Epidemic Intelligence Officer, Communicable Disease Center, Public Health Service, assigned to the Los Angeles City Health Department (Emmett). Epidemiologist, Los Angeles City Health Department (Chapman).

on a culture of the stool. Dietary measures, supportive treatment and chloramphenicol therapy were instituted. Diarrhea gradually abated and no organisms grew on cultures of the stools.

The patient did not gain weight, however, and two weeks later had another episode of diarrhea, the cause of which was not determined. This responded to symptomatic treatment, but despite this, the infant did not gain weight and died on the 48th day of life.

Until the first attack of diarrhea the infant had been in the premature nursery under conditions of strict isolation in a well-managed nursery. He was taken to the operating room from the premature nursery and was returned to the premature nursery immediately after operation.

No other cases of infant diarrhea were observed in that nursery or on the same floor at that time or within the maximum incubation period of salmonellosis. Rectal swab cultures were taken on all the doctors, nurses and attendants who had handled the baby since admittance, including physicians and nurses who had carried out and assisted at the operation. All cultures were negative for salmonellae.

Members of the household into which the baby was born were examined and rectal swab cultures obtained from both parents and two siblings. S. typhimurium was recovered from the mother on three occasions. The infant was born at home where it remained five days and received formula feedings prepared by the mother, occasionally by the father.

After admittance to hospital, the infant was isolated and never in contact with family members. Therefore infection is most likely to have occurred at home during the first five days of life. The time elapsed from the last day at home to the onset of diarrhea was eleven days. Infection could have occurred at birth, which would make the incubation period sixteen days. The significance, in this regard, of the lack of continuity between stomach and small intestine cannot be ascertained. The incubation period usually recorded for endemic cases of Salmonellosis ranges from one to seven days, and in food-borne outbreaks from six to 48 hours.

## SUMMARY

A case of Salmonella typhimurium infection causing severe diarrhea in a premature infant with complete atresia of the duodenum, surgically corrected, is presented. Epidemiological evidence indicated the mother was the source of the infection and placed the minimum incubation period at eleven days, the maximum incubation at sixteen days.

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California MEDICINE

# EDITORIAL

## Antiquated Industrial Fees

INDUSTRIAL MEDICAL and surgical fees, long a bone of contention in California, came again into the limelight last month, when an interim committee of the State Senate devoted particular attention to them. As a result, medicine had its first opportunity in years to present a review of the history of such fees and to point out the present predicament of the doctor in trying to obtain adequate payment for his vital services in industrial accident cases.

Oddly enough, the physician is recognized by all concerned as the keystone in handling all industrial accident cases but is nonetheless lightly brushed aside by all other parties when the value of his services is considered.

To the injured workman, the physician is the skilled practitioner who heals his injuries and restores him to full vigor and function; at the same time, the physician is treated as a "company man" who is ever ready to testify disparagingly on the workman's claim for compensation payments. To the insurance carrier, the doctor is a supplier of services which are bought in a competitive market, to the financial advantage of the corporation underwriting the risk. To the Industrial Accident Commission, the physician is a necessary element in each case but still a self-sufficient individual who must look to himself to secure just payment for his services. To the state Insurance Commissioner, the doctor is merely a bargaining agent whose demands for compensatory fees may result in increased premium rates for disability insurance.

This unenviable position has forced physicians to enter the bargaining market in an effort to obtain proper payment for their services. Now, for the first time, the doctors of California have available the type of economic information required for such bargaining.

Starting in 1950, a special committee of the California Medical Association went about a systematic program of studying the economics of industrial medical practice. Business indices, cost of living figures, wage bases and other economic factors were studied. The moral basis for setting industrial injury fees was considered, as were the historical facts in industrial practice and the common-sense factors in a system greatly enlarged since its beginning in 1914.

Out of these studies has come the realization, unbelievable to some and unacceptable to others, that industrial medical fees have lagged far behind the economic trends which affect all other fees and prices. The doctor handling industrial cases is, bluntly, being discriminated against in terms of economic justice.

Industrial fees, as stated in an official 1918 fee schedule, were based at that time on the fees which physicians might expect to receive from private patients with an average annual income of $1,250. With the average for all covered employees today at more than $3,700 annually, the doctor might expect about a 200 per cent increase in such fees. Instead, he shows about an 80 per cent increase.

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For information on preparation of manuscript, see advertising page 2

Is the physician's fee based upon his cost of operating his practice? If so, he is again from ten to twenty years behind the economic wave in his industrial fees. Is his fee based on cost of living figures? If it is, the industrial part of his practice is in the red.

The C.M.A. committee, armed with this information, has now come up against the bleak realities of trying to get official recognition of industrial fees in keeping with the times and the economic forces operating in all other parts of the industrial insurance picture. Between the Insurance Commissioner, the Industrial Accident Commission and the insurance carriers, the doctor is left to shift for himself, for none of them are willing to face up to the fact that industrial fees must be radically adjusted if they are to be made equitable and set at a level where the vast majority of California physicians can and will handle industrial accident cases.

Under this squeeze, the C.M.A. committee has suggested two possible moves. First would be the attempt to secure legislation placing the responsibility and authority for establishing an industrial fee schedule squarely in the lap of a state authority. Second would be the possible drafting of an adequate fee schedule which would be recommended for use by all physicians whether it did or did not carry the approval of any of the state agencies or the insurance carriers.

Both these suggestions are fraught with pro and con considerations. Both include elements which are not easily palatable to physicians. Both have inherent dangers which might bring about their failure. On the other hand, if bargaining across the table offers no more chance for success than has heretofore been demonstrated, radical alternatives may be indicated.

If justice to all is to prevail, common sense would dictate the objective consideration of this problem by all concerned, with a view toward a swift and equitable settlement with the least possible disruption of existing relationships.

## 1953 Annual Session

PRECEDENT WILL BE broken in the C.M.A. 1953 Annual Session, when the familiar four-day meeting will give way to a five-day program.

As now planned, Sunday and Wednesday, May 24 and 27, will be reserved for meetings of the House of Delegates, with no Association scientific meetings scheduled for either day. On Monday and Tuesday, both general and sectional meetings will be held, and on Thursday additional sectional sessions will convene. Wednesday will also be set apart for meetings of the other medical organizations, including heart, chest, industrial and other groups. The day will likewise be available for medical golfers, for visiting scientific and technical exhibits and for such other business as visiting members may have.

The proposed program will allow the House of Delegates more time for the transaction of its business, a sorely needed provision in light of the harried schedule presented to that body in recent years. It will also allow reference committees more time for hearings and deliberations and members of the House time to attend at least some of the scientific sessions. It will permit a more orderly scheduling of all sessions and, simultaneously, it will permit any member to attend the session for only four days without losing important programs if his own schedule is crowded.

In its augmented size, the C.M.A. for several years has faced the need for organizing its annual session on a broader basis, for the benefit of both business and scientific functions. The five-day meeting seems to be the answer.

## C.M.A. INTERIM SESSION, DECEMBER 6-7

Mark Hopkins Hotel, San Francisco

### SCIENTIFIC PROGRAM

**Symposium on Burns**

Present Concepts in the Treatment of Acute Burns—William A. Todd, Jr., Colonel, MC, USA, chief of surgical service, Letterman Army Hospital, San Francisco.

Fluid and Electrolyte Problems Relating to Burns—James Hopper, Jr., M.D., director of clinical laboratories, University of California Hospital, and assistant professor of medicine, University of California School of Medicine.

California MEDICAL ASSOCIATION

# NOTICES & REPORTS

## The Health Needs of the Nation

L. A. ALESEN, M.D.,
*President of the California Medical Association*

DR. ALESEN was invited by The President's Commission on the Health Needs of the Nation to discuss the following questions, prepared by the Commission, at a regional meeting held in San Francisco, September 29, 1952.

1. What are the principal unmet health needs in this area?
2. What can be done to meet those needs?
3. How can prepaid medical care be best provided?
4. How much government in medical care?
   (a) Veterans Administration
   (b) For military dependents
   (c) Hospital construction
   (d) In the care of psychotics, tuberculous and the aged

GREAT STRESS is currently laid upon medical economics. It is contended that the cost of good medical care is so great that large segments of our people are unable to afford it, and therefore are deprived of their rightful opportunity to good health and well-being. Since medical economics is just one phase, albeit an important one, of the economic process in general, it would seem relevant to begin a discussion of the subject with some broad general observations on economic fundamentals and subsequently to apply such observations more specifically to the problem of good scientific medical care for every citizen in this country.

It has always been one of the prideful goals and traditions of American medicine to place within the reach of every individual in this country the best grade of medical care at a price that individual can afford to pay, whether that be a high fee, a low fee, or no fee at all. That this goal has in large measure been achieved is attested by the fact that the American people are the healthiest people in the world today, bar none, when comparable populations are considered. Further, under our system of the private and competitive practice of medicine as an integral part of the American system of profit and loss, we have made strides in our profession comparable to the marked developments in industry and business and for exactly the same reasons. The sulfa drugs, the antibiotics, improved techniques for diagnosis, anesthesia, surgical procedures, and the marvels of internal medicine find their current counterparts in electronics, jet propulsion, and atomic fission.

Economics is defined as the science of the production, the distribution and the consumption of goods and services; or a study of the way man makes his living. The ideal state of economic health would be an economy in which there are readily available the greatest amount and variety of goods and services to every individual living within the economy, at a price well within his reach and in an environment in which he finds encouragement to produce to his utmost, to consume, to distribute, and to accumulate the products of his labor. The fact that during the six thousand years of recorded history there have been a few instances in which this definition of the ideal economy has been met is significant. The fact that these instances have been short-lived and the

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reasons for their termination have particular importance for this discussion.

History teaches one outstanding and never-failing lesson: Social and economic structures have been productive, strong, and expanding when group or government action has been limited to its appropriate biologic function—that of protection of the individual in the enjoyment and accumulation of the fruits of his labor. Under such social and economic organizations, individual responsibility has been paramount: *individual reward for individual merit; individual penalty for individual failure* have been recognized as inviolable. However, in practically all of the human societies, sooner or later the collectivist has insinuated his siren song of group action, and immediately thereupon the process of disintegration and decay has commenced. Historians tell us that there have been approximately 2,500 instances of the communistic or collectivistic state in the world's history, without a single instance of success unless one wishes so to designate present day Russia.

Over the past fifty years in America, because of the application of tools and the use of constantly improving techniques, our productivity has increased on the average of about 3 per cent per year. By and large, that increased productivity has over the years been well distributed. A few examples will show how well.

In Russia, under communism, the workman can buy one-third quart of milk with his hour's labor. In England, under socialism, he can buy three quarts. In America, under private enterprise, his hour's labor will buy him six quarts of milk. In Russia, under communism, the individual has available 40 square feet of housing. In England, under socialism, he has 105 square feet. In America, under individual enterprise, he has 410 square feet of housing. In Russia there is three-quarters of one telephone per one hundred persons. In Great Britain there are eight telephones. In America there are 22 telephones per hundred persons. In Russia, the workman can buy one-half pair of shoes for one week's work. The American workman can buy six pairs of shoes. The Russian workman can buy one-half suit of clothes for one month's work. The American workman can buy four suits of clothes. In the United States there are approximately eighty million life insurance and annuity policy holders with a total of approximately two hundred fifty billion dollars of such protection all developed under our competitive system. Over seventy million Americans have bank accounts.

With 6 per cent of the world's population, Americans enjoy 94 per cent of the television sets, 92 per cent of all bathtubs, 85 per cent of all automobiles, 54 per cent of all telephones, 48 per cent of all radios. Our 6 per cent of the world's people consume 65 per cent of the world production of corn, 60 per cent of petroleum, 60 per cent of wheat, 53 per cent of wool, 48 per cent of coffee, and 45 per cent of meat.

The American Federation of Labor compiled a report on comparative real wages just before World War II. This report stated that in America the workman's hour's work would buy him 3.8 market baskets of groceries; in Denmark 2.18; in Great Britain 1.8; and in Italy .96.

A proper question is as to whether or not the laboring man has in fact benefited by this increased productivity. This question is answered by figures recently released by Mr. Joe Hertel,[1] Farm Advisor, University of California College of Agriculture and United States Department of Agriculture, San Bernardino, which speak eloquently on this subject: "In 1929, the average wage earner in the United States received 56 cents per hour. In 1951 he received $1.60 per hour. In 1929 he had to work 47 minutes to buy a pound of round steak which required 41 minutes in 1951. He works 29 minutes now to buy a pound of pork chops for which he labored 39 minutes; 9 minutes to buy one quart of milk as compared to 15 minutes; 21 minutes to buy one pound of poultry meat in 1951 compared to 41 minutes in 1929; and, only 25 minutes to buy a dozen eggs for which he labored 54 minutes in 1929; and, he gets one pound of turkey for 22 minutes of work as compared to 55 minutes in 1929."

Just how much more might have been accomplished had we not during this period of time been impeded in our economic progress by all manner of government interferences as well as by the strictures interposed by sit-down strikes, featherbedding tactics, and sabotage?

Turning now to the application of fundamental economic principles to the problem of good medical care, it would first seem pertinent to determine just what portion of the American family budget is actually required for good medical care, and whether or not the average family is in fact being deprived of good care because of high cost.

In the year 1950, the American people spent eight billion dollars for all types of medical care, this representing 4.4 per cent of the $193,600,000,000 that they spent for all goods and services in that year.[2] Over the years, the outlay for medical care has varied from 4.1 per cent to 4.4 per cent as noted in 1950.

In 1950, the American people spent 5.8 per cent for recreation, such as football, baseball, and other spectator amusements, theater admissions, bowling, horse-racing. They spent 4.2 per cent for alcoholic beverages or only a trifle less than for all types of medical care. They spent 2.3 per cent of their budget

on tobacco; 1.2 per cent on barber shops, beauty parlors, baths, massages, toilet articles and cosmetics; and 0.8 per cent on jewelry, clocks, watches, and their repairs. Thus, it would seem that, mathematically at least, the expenditure of three times as much for alcohol, recreation, and tobacco as for medical care would not justify the contention that medical care is out of the reach of the average citizen.

During the twenty years between 1930 and 1950, some variation occurred in the way our people spent their medical dollar. In 1930, the physician got 32 cents of it, now he receives 28 cents of it, an actual decrease of 12.5 per cent. In 1930, dentists got 16 cents out of the dollar, now they get 12 cents or 25 per cent less. In 1930, 19 cents of the consumer's medical dollar went for drugs, in 1950, only 17 cents, a drop of 10.5 per cent. Fourteen cents of the consumer's dollar in 1930 went to the hospitals whereas in 1950, 23 cents was so consumed, or an increase of 64.3 per cent. This is a marked increase but there are certain offsets and explanations of these figures which make hospital care not so high relatively as it would appear at first glance.

The cost of all goods and services purchased by consumers rose 72 per cent between 1930 and 1950.[3] On the same scale, hospital rates increased 135 per cent, but physicians' fees were up only 40 per cent, and surgeons' and specialists' charges up only 41 per cent.

During that same base period, the average weekly earnings of production workers in manufacturing industries rose 165 per cent.

Translating these facts into terms of real wages, that is, the purchasing power of the consumer's services in terms of medical and hospital services, some interesting conclusions are reached. In 1950, the individual needed to work only 53 per cent as long to buy the same amount of physician services as he was required to do in 1935 to 1939. Hospital charges in 1950 were high, but the patient could buy as much care as in the base period with only 89 per cent as much work.

In connection with hospital care, several facts are often overlooked. In the first place, for each patient in the modern hospital, approximately two and one-half employees are required, the payroll for labor alone thus constituting about 70 per cent of the hospital bill. Also, as is well known, hospital costs of food reflect in a large measure an important component of labor. During the past twenty years, something of a minor revolution has occurred in the efficiency of hospital bed use. Whereas twenty years ago the average hospital bed accommodated about twenty patients per year, now the same bed will care for approximately forty patients. In addition, the modern developments of earlier and better diagnosis, improved anesthesia, surgical and operating-room techniques, the use of antibiotics, sulfa drugs, transfusions, have all combined to get the patient out of the hospital more completely recovered in much less time. Therefore, the total expenditure for hospital care occupies a fairly favorable relative position. This same increased efficiency in the use of modern techniques in diagnosis and treatments has greatly enhanced the efficiency of the individual physician, it being estimated that each physician in 1950 rendered approximately 50 per cent more care than during the 1935-1939 base period.

On the question of the alleged shortage of physicians and the need to subsidize medical schools, it should be borne in mind that since this base period the population has increased about 17 per cent, whereas the number of physicians has increased by 22 per cent in the same period. Thus, statistically, the position of American medicine is on a very firm economic foundation. The well-known figures on rapidly lowering death rates and decreased morbidity in all of the major conditions with the exception of the degenerative diseases shows that the American people are in fact receiving the advantage of the improved techniques and have in fact not been barred by any alleged economic obstacle.

#### ANSWERS TO THE FOUR QUESTIONS

With more specific reference to your four questions, it is our belief in response to question number 1, that there are no major unmet health needs in this area. The State Chamber of Commerce is at this time conducting a survey to ascertain the extent to which the people of this state are covered by voluntary prepayment plans for the cost of medical care. It is our opinion that at least six million of the state's eleven million are so covered in some manner at least. Our own Blue Shield and Blue Cross plans together with the many excellent indemnity plans written by the private insurance companies have made and are making rapid strides toward removing the economic shock from illness. In this connection, notice should be taken of the excellent work done for the indigent patient in our large metropolitan centers by county hospitals, medical schools, and charity clinics, medical care being in many instances rendered without any charge whatsoever.

Some idea of the value of this care may be gained from the estimate made of the services rendered by members of the Los Angeles County Medical Association to the indigent sick at the Los Angeles County Hospital during the year prior to World War II. Using minimum fees as the basis of such estimate, the figure of fifteen million dollars for those services was estimated. When it is remembered that the total budgetary outlay for the institution for the

year was six and a half million dollars, the value of these free services in comparison looms large if the taxpayer had been required to pay for them at the usual rates.

It is recognized that there are some rural areas where the health needs are not met with complete satisfaction although these gaps are being rapidly closed. Further, the problem of medical care for the migrant farm worker is a difficult one, and one that has not been solved completely as yet. There are many factors involved, not the least important of which is the irresponsibility of the workers themselves. The Committee on Rural Health of the California Medical Association is giving this whole problem careful study and is prepared to make constructive recommendations in the near future.

2. What can be done to meet those needs? Certainly an expansion of any and all legitimate and responsible plans for the voluntary prepayment of the costs of illness ought to be encouraged. Just as free and unrestricted competition in the life insurance and annuity field has resulted in the coverage of most of our citizens, so will the same type of enterprise produce the same salutary results in the field of voluntary health insurance provided too many roadblocks are not interposed.

However, a broader and more comprehensive answer to this question would seem to be in order. Just as the ideal economic state is one in which there is a maximum production and distribution of goods and services without artificial let or hindrance, so is the ideal system of medical care, and there is an inescapable relationship between the two subjects, for medical care is inseparably integrated in our system of profit and loss or free enterprise. If we are really sincere in our desire to give to the American people the best medical care at a price they can afford to pay, then we must recognize that government restrictions upon and intervention in the economic process in any manner whatsoever reduce the amount and availability of all goods and services. Price and wage controls, crop subsidies, agricultural allocations, rent control, all restrict the free flow of goods and services in such a manner as to deprive every citizen of the just and reasonable share to which he would be entitled if he were allowed to participate in a free economy unrestricted by any government order whatsoever except that required to protect him from the predatory activities of his fellows. Government manipulation of the currency, arbitrary abolition of the gold standard, and one hundred and one other capricious and unwarranted interferences with the economic and social freedom of the citizen all work toward a decrease of output and therefore a decrease in the availability of all the good things of this life, medical care being one of them. But this is heady wine, and of course far too strong a potion for our current voters who have been conditioned by forty years of indoctrination for the Welfare-Police-Slave State. It will take another forty or fifty years of hard work to return our country to any semblance of economic and social sanity.

3. How can prepaid medical care be best provided? This question is best answered by the foregoing statement. It is our belief that there is no place for compulsion in any of these programs. A word is in order concerning a difference of opinion which exists in the prepayment field, some advocating complete or full coverage and others partial coverage or indemnification.

In any form of voluntary prepayment of the costs of illness, the insured person must be thoroughly aware of the cost of the service and must be responsible for its intelligent and economic usage. Certain restrictions upon abuses, such as payment for the first two or three visits in any given illness, are essential. More recently, a type of deductible insurance comparable to that employed in the automobile field has developed. This would seem to offer great possibilities inasmuch as the average individual does not require aid in the payment of minor bills but only in the case of catastrophic illness.

4. How much government in medical care?

a. *Veterans Administration.* The medical activities of the Veterans Administration have always posed a serious problem to the private practitioner of medicine. Recognizing that at least 80 per cent of those now receiving care in the Veterans Administration hospitals are there because of non-service connected disabilities, it seems imperative that some means be provided whereby this unfair burden be removed from the shoulders of the taxpayer and its unfair competition be removed from the private practitioner of medicine. If the veteran with a non-service connected disability is in fact indigent and unable to pay for this care, he is quite properly the ward of his local city or county political unit and should receive care at its hands. If, on the other hand, he is not an indigent there is no reason why he should be occupying a bed and receiving care in a government hospital for a non-service connected disability.

b. *For military dependents.* It is believed that care can best be provided for military dependents by an expansion of the Blue Cross, Blue Shield, and private indemnity medical care plans.

c. *Hospital construction.* In many instances, the effect of subsidization by federal money through the Hill-Burton Act and/or state money has been so to increase the cost of such construction by the imposition of numerous and often unnecessary and illogical requirements, that the individual community benefits little if any from the subsidy. In addition, the

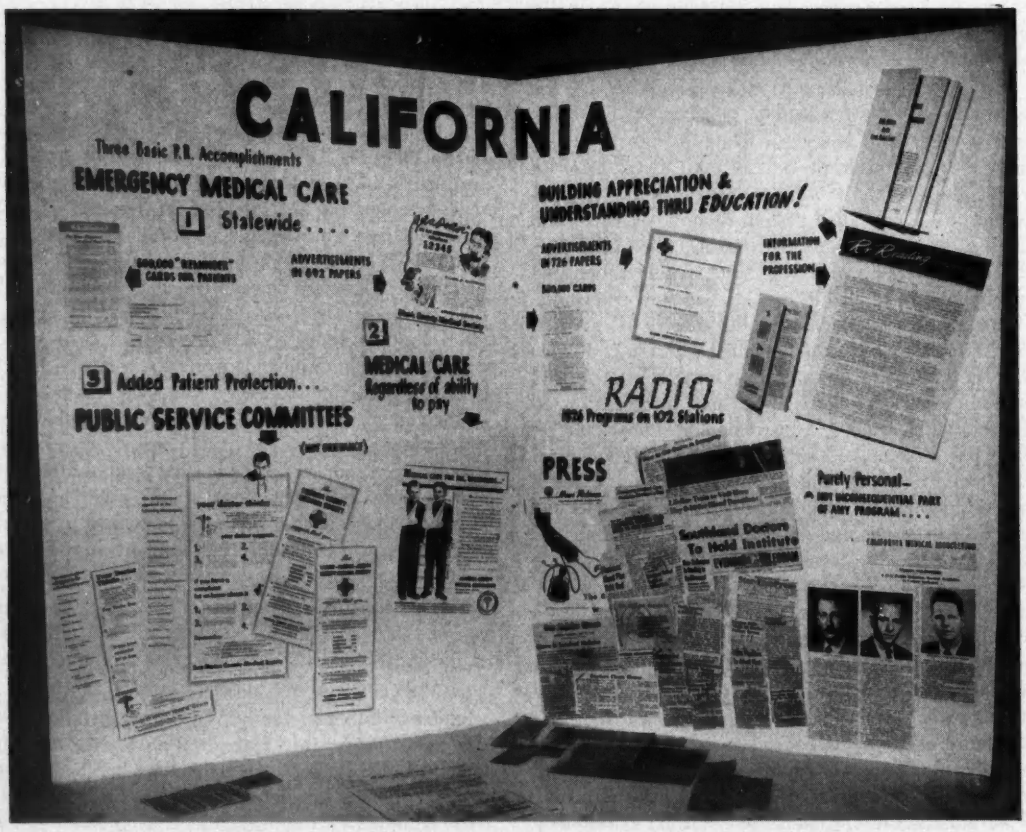
community is often encouraged by the lure of such money which seems to be free, to build out of proportion to its needs and to find when the hospital is constructed that a white elephant is upon its hands with no means for its maintenance.

d. *In the care of psychotic, tuberculous, and aged patients.* At present, by far the greatest percentage of psychotic and tuberculous patients receive care in state or county institutions. This is not an ideal situation, but it is one which has seemed to develop as a matter of necessity. The present care of the aged in rest homes and sanitariums, and other makeshift domiciles is far from satisfactory. If we would remove from our economic system the present strictures to full production under which it labors, it ought to be possible in very short order so to increase our production throughout the economy as a whole as to provide under the private enterprise system ample care for all of these unfortunates. As proof of this, James F. Lincoln's "Incentive Management" is an excellent example of what can be done when private enterprise is really given an opportunity.

In view of the expansion of voluntary health insurance—in view of the expansion of hospital facilities in California in the last few years, coupled with the tremendous technical improvements that have shortened the duration of hospital stays and which have had the effect of doubling hospital capacity without increasing the number of beds—and in view of the number of physicians practicing in the state and their distribution, we submit that this area does not have any major unmet medical needs and there is no necessity or desirability for any additional federal legislation.

#### REFERENCES


1. Hertel, Joe, Farm Advisor, University of California College of Agriculture and United States Department of Agriculture, San Bernardino.
2. Dickinson, Frank G., *Bureau of Medical Economic Research of the American Medical Association*, M-56.
3. United States Bureau of Labor Statistics.


PR ON PARADE— California's physicians received a fair share of recognition when this exhibit, pictured above, was viewed recently by some 250 medical society executives at the AMA's Public Relations Institute in Chicago. Prepared by the CMA's PR Department, it portrays medicine's accomplishments, statewide, in varied but related activities.

# CALIFORNIA MEDICAL ASSOCIATION

# Annual Meeting

## LOS ANGELES
## May 24-28, 1953

### *Scientific Exhibits*

The space available for scientific exhibits is limited. If you would like to apply for space, please write immediately to the office of the California Medical Association, 450 Sutter Street, San Francisco 8, for application forms. To be given consideration by the Committee on Scientific Work, the forms, completely filled out, must be in the office of the California Medical Association not later than December 1, 1952. (No exhibit shown in 1952, and no individual who had an exhibit at the 1952 session, will be eligible until 1954.)

### *Motion Pictures*

At the coming annual meeting of the California Medical Association, to be held at the Biltmore Hotel, Los Angeles, May 24-28, 1953, approximately 100 motion pictures, on surgery and medicine, will be shown on the program of the Motion Picture Division.

The educational and scientific value of motion pictures has been proven by the large attendance at the Motion Picture Section during our previous meetings.

If you would like to present a motion picture film on this program, it is imperative that you submit your application before January 2, 1953.

Address all communications to:

ARTHUR E. SMITH, M.D., D.D.S.
Chairman, Motion Picture Division
California Medical Association
1930 Wilshire Boulevard, Suite 511, Los Angeles 5, Calif.

# — In Memoriam —

DAVIS, STANLEY S. Died in Oakland, September 13, 1952, aged 45, of myocardial infarction. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1932. Licensed in California in 1932. Doctor Davis was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and the American Medical Association.

✤

DIEPENBROCK, ANTHONY B. Died in San Francisco, September 16, 1952, aged 64, of melanosarcoma. Graduate of Harvard Medical School, Boston, 1912. Licensed in California in 1912. Doctor Diepenbrock was a member of the San Francisco Medical Society, the California Medical Association, and the American Medical Association.

✤

DUFFICY, GEORGE W. Died in Sacramento, August 31, 1952, aged 80, of cerebral accident. Graduate of the University of California Medical School, Berkeley-San Francisco, 1898. Licensed in California in 1898. Doctor Dufficy was a retired member of the Sacramento Society for Medical Improvement, the California Medical Association, and the American Medical Association.

✤

HYLAND, CLARENCE M. Died in Apple Valley, August 29, 1952, aged 66, of coronary thrombosis. Graduate of Creighton University School of Medicine, Omaha, 1916. Licensed in California in 1927. Doctor Hyland was a member of the Los Angeles County Medical Association, and the American Medical Association.

✤

JONES, ARCHIE A. Died in Long Beach, September 20, 1952, aged 54, of coronary artery disease. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1927. Licensed in California in 1927. Doctor Jones was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

POOLE, FENN E. Died in an automobile accident in Los Angeles, September 21, 1952, aged 46. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Poole was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

SAELTZER, DUDLEY V., JR. Died in Sacramento, September 13, 1952, aged 46. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Saeltzer was a member of the Sacramento Society for Medical Improvement, the California Medical Association, and the American Medical Association.

✤

SILVERMAN, DORA J. Died June 14, 1952, aged 61. Graduate of National University of Arts and Sciences Medical Department, St. Louis, Missouri, 1914. Licensed in California in 1922. Doctor Silverman was a member of the Los Angeles Medical Association, the California Medical Association, and the American Medical Association.

# Q. & A. on C.P.S.

*Question:* **Recently, in the case of a patient who was referred to me by another physician, I noticed that C.P.S. had deducted the first two visits when payment was made for my services. This does not seem right in view of the fact that the patient had been seen two or three times by the first (referring) physician.**

*Answer:* As stated in the question, this situation appears to indicate an error on the part of C.P.S. However, it is likely that the C.P.S. error resulted from an incomplete billing having been submitted by the physician.

When a case is referred from one physician to another, this should be indicated in the space provided on the C.P.S. billing form. Otherwise, C.P.S. has no knowledge of the referral and, consequently, might easily make the error of deducting the first two visits from the payment made to the second physician.

*Question:* **Is it always necessary to have the patient fill out the top portion of the billing form?**

*Answer:* No, this is not mandatory, although it is certainly advisable as a means of determining whether the patient is over or under the C.P.S. income level. In some instances, the physician may already know the patient's income status and thus does not need the information. If there is any doubt about the income, however, the patient should be asked to complete the top portion of the billing form; and it should always be done in case of new patients.

*Question:* **As a radiologist I do referral work under the Veterans Program for other physicians. I have been unable to obtain payment recently in several cases although, apparently, the veteran was eligible for treatment.**

*Answer:* The attending physician should request the service in advance and wait for his authorization and referral form prior to sending the veteran to your office. The veteran should present the referral form to you. It specifies the procedure and the fee that will be paid by the Veterans Administration.

It is important in order to obtain payment that this service be performed within the period of time stated on the referral form. Payment cannot be obtained if service is not requested by the attending physician or authorized by the Veterans Administration. C.P.S. cannot obtain payment if the services are not performed within the prescribed period. A medical report should be submitted with the billing.

In emergencies, or where there is a need for prompt treatment, the Veterans Administration will accept collect telephone calls and give verbal approval for the procedure if the veteran is eligible.

*Question:* **Do C.P.S. fees for surgery include any payment for preoperative care or visits?**

*Answer:* No. C.P.S. benefits under the surgical contract *begin at the time surgery is performed.* Consequently, any services rendered prior to the time of surgery are not included in the fee for surgery. Instead, they are payable under the patient's medical coverage, if the patient has medical coverage and if the services are benefits of the medical contract. If the patient does not have medical coverage, or if the services are not covered by the medical contract, the physician should bill the patient for preoperative care.

*Question:* **Should a physician's bill for C.P.S. work be submitted each month, even if treatment of a patient is not completed and will continue into the next month?**

*Answer:* Yes, bills for C.P.S. work should be submitted monthly—without regard to whether the services rendered to a particular patient are completed.

A separate billing is required for each patient, even for members of the same family; and all bills should be submitted to C.P.S. by the 15th of the month in order to expedite payment.

*Question:* **Do all C.P.S. members have their own C.P.S. identification cards?**

*Answer:* No. Two cards are issued to each beneficiary member and both bear the name of the beneficiary member. One card is for use by the beneficiary member, the other for use by the dependents. The coverage which the beneficiary has is indicated by code numbers which appear in the squares under the heading "beneficiary." Coverage for dependents is indicated by code numbers which appear in the squares under the heading "dependent." Explanations of code numbers in terms of coverage are provided in the Physician's Manual.

*Question:* **What fee schedule is now being used by C.P.S.?**

*Answer:* The fee schedule under which payments to physicians are made is the one dated September 1, 1949.

(In 1951 a proposed fee schedule was distributed to physicians for their consideration. However, this schedule is not in use and should not be used by physicians in billing or in determining what the C.P.S. payment on a particular service will be.)

# NEWS & NOTES

## NATIONAL · STATE · COUNTY

### ALAMEDA

**Dr. Ergo A. Majors** of Oakland recently was honored at a dinner at the Claremont Country Club for completion of 50 years of practice. Graduated in 1902 from Toland Medical College, Dr. Majors passed the first examination to be given by the California State Board of Medical Examiners.

Dr. Albert Meads was toastmaster at the dinner, and speakers were Joseph Knowland, publisher of the Oakland *Tribune*, Dr. Cyril J. Attwood, president of the Alameda-Contra Costa Medical Association, Dr. John Sherrick, and Dr. Gerald Crenshaw.

### LOS ANGELES

**Dr. Ian Macdonald** of Los Angeles, who served during the past year as vice-president of the California Division of the American Cancer Society, recently was presented with the Society's national medal for distinguished service in the field of cancer control.

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Almost 500 physicians attended the fourth annual **postgraduate assembly** sponsored by the staff of **St. John's Hospital**, Santa Monica. Out-of-state speakers at the three-day meeting, held September 8-10, were Dr. Oliver Cope, professor of surgery at Harvard Medical School; Dr. Stewart Wolf, head of the department of medicine, University of Oklahoma; Dr. W. A. D. Anderson, professor of pathology at Marquette University, and Dr. Leo Rigler, professor of radiology at the University of Minnesota.

The program was arranged by Dr. John C. Eagan, director of the postgraduate assembly.

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Appointment of **Dr. John Gardner** as health officer for the Bellflower Health District was announced recently by Dr. Roy O. Gilbert, Los Angeles County health officer.

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**Dr. Percy Grover** of Van Nuys was elected Surgeon General of the Veterans of Foreign Wars at the 53rd National Encampment of the organization. He had served three years as surgeon of VFW in California.

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An organizational meeting of the Southern California District Branch of the **American Psychiatric Association** will take place Friday, November 14 at 8 p.m. at the Institute of Aeronautical Sciences, 7660 Beverly Boulevard, Los Angeles. All A.P.A. members are cordially invited to attend.

### SAN DIEGO

Appointment of **Dr. Berenice I. Stone** as a member of the California State Board of Social Work Examiners was announced recently by Governor Earl Warren.

**Dr. Werner Lehmann,** who recently completed an 18-month tour of duty in the Army, has resumed practice in San Diego. Before he entered the Army he practiced at Hotel del Coronado.

### SAN FRANCISCO

Grants totaling $20,129 to support eleven **consultative tumor boards** in nine San Francisco hospitals were awarded recently by the county branch of the American Cancer Society. The recipients and the amounts each received: San Francisco Hospital, $3,660 for two boards; University of California Hospital, $4,120 for two boards; Stanford Hospital, $2,902; Mt. Zion Hospital and French Hospital, $1,500 each; Mary's Help, $1,400; St. Mary's, $1,327; St. Luke's, $1,320; St. Joseph's, $1,200.

* * *

**Stanford University Medical School** has established a new position in its Department of Public Health and Preventive Medicine for an assistant professor of statistics. Lincoln E. Moses, Ph.D., has been appointed to the position and will serve half-time in the School of Medicine and half-time in the Department of Statistics in the School of Humanities and Sciences. Dr. Moses will participate in the teaching of the medical students, working toward the integration of statistical reasoning and methods in all of the departments but will devote himself primarily to consultations on evaluation and interpretation of observations in research, and the design of experiments, for divisions in the Medical School.

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The 1952 American Cancer Society Award for distinguished service in cancer control was received jointly by **Dr. Herbert F. Traut,** professor of obstetrics and gynecology in the University of California School of Medicine, and **Dr. George Papanicolaou** of Cornell University. Dr. Papanicolaou was cited for discovery of the exfoliative cytologic method of detecting the presence of cancer, and Dr. Traut for "collaboration in the demonstration of the clinical significance" of the method and for having "substantially reduced the interval between discovery and general application."

* * *

**Dr. Robert Wartenberg,** clinical professor of neurology, University of California School of Medicine, has been elected a corresponding member of the German Society of Neurology.

### SAN MATEO

**Sequoia Hospital** recently received American Medical Association approval as a hospital for residency training for general practice. The hospital had previously been notified it was qualified to provide residency training for nurses and administrative personnel.

### STANISLAUS-MERCED-MADERA

**Dr. Robert J. Garbarino** has been appointed director of the Ahwahnee Sanatorium in Madera County which is operated jointly by Stanislaus, Merced and Madera counties. He had been acting director since July 1 when Dr. Gordon A. Diddy resigned the post to become director of tuberculosis control for Fresno County.

### TULARE

**Dr. Erwin P. Brauner,** formerly of Long Beach, became Tulare County health officer September 1. He succeeded Dr. Wayne Powell, who was inducted into the armed forces.

# POSTGRADUATE EDUCATION NOTICES

## COLLEGE OF MEDICAL EVANGELISTS

**Part-time Refresher Courses 1952-1953**

Anesthesiology (4 months). Full time. Vacancy occurs each two months. Facilities limited to two students. Tuition: $300.00. Dr. Forrest E. Leffingwell and associates.

Genito-Urinary Diseases. Daily: 10:00 a.m. to 2:00 p.m., Nov. 17 through 21, 1952. Tuition: $60.00. Classes are conducted at the Ambassador Hotel, Los Angeles, under the auspices of the Los Angeles Urological Society.

Surgical Diseases of the Peripheral Vascular System (8 periods). Tuesdays: 7:00-8:30 p.m., Jan. 6 through Feb. 24, 1953. Tuition: $30.00. Dr. Carl H. Talmadge and associates.

Differential Diagnosis of Internal Diseases (12 periods). Tuesdays: 8:00-9:30 p.m., Los Angeles County General Hospital. Jan. 6 through March 24, 1953. Tuition: $50.00. Dr. Julius Bauer.

Diseases of the Chest (2 days). Thursday and Friday, Los Angeles County Medical Association. Jan. 22 and 23, 1953. Tuition: $15.00. Lecturers to be announced.

Dermatology (12 periods). Wednesdays: 8:00-9:30 p.m., Jan. 7 through March 25, 1953. Tuition: $40.00. Dr. Clement E. Counter and associates.

General Urology (9 periods). Wednesdays: 8:00-9:30 p.m., Jan. 7 through March 4, 1953. Tuition: $35.00. Drs. Roger W. Barnes, R. Theodore Bergman, and associates.

Proctology (10 periods). Thursdays: 8:00-10:00 a.m., Jan. 8 through March 12, 1953. Tuition: $50.00. Dr. Malcolm R. Hill and associates.

Otolaryngology (8 periods). Tuesdays: 8:00-9:30 p.m., Feb. 10 through March 31, 1953. Tuition: $30.00. Dr. H. James Hara and associates.

Histology and Histopathology of the Eye (15 periods). Wednesdays: 7:30-9:30 p.m., Feb. 25 through June 3, 1953. Tuition: $60.00. Dr. I. G. Sommers.

Varicose Veins (6 periods). Tuesdays: 7:00-9:00 p.m., March 3 through April 21, 1953. Tuition: $25.00. Dr. Carl H. Talmadge and associates.

Gynecology (10 periods). Wednesdays: 8:00-9:00 a.m., March 25 through May 27, 1953. Tuition: $30.00. Dr. Dell H. Haughey and associates.

Operative Surgery (8 periods). Tuesdays: 7:00-9:00 p.m., April 7 through May 26, 1953. Tuition: $150.00. This course in operative surgery will be a combined lecture and laboratory course designed to provide opportunity for the student physician to personally perform standard major operations. Dr. Harry A. Davis.

Endocrinology (8 periods). Tuesdays: 8:00-9:30 p.m., Los Angeles County General Hospital. April 7 through May 26, 1953. Tuition: $30.00. Dr. Julius Bauer.

Thoracic Surgery (8 periods). Wednesdays: 8:00-9:30 p.m., April 15 through June 3, 1953. Tuition: $30.00. Dr. Lyman A. Brewer.

Minor Orthopedic Surgery (8 periods). Thursdays: 8:00-9:30 p.m., April 16 through June 4, 1953. Tuition: $30.00. Dr. Alonzo J. Neufeld.

Diseases and Injuries of Bones and Joints. Full time. July 6 through 31, 1953. Tuition: $100.00. Drs. G. Mosser Taylor, Alonzo J. Neufeld, and associates.

Contact: For further information, write Chairman, Section on Graduate and Postgraduate Medical Education, College of Medical Evangelists, 312 North Boyle Ave., Los Angeles 33, Calif.

## GENERAL

The sixth annual meeting of the **Western Society for Clinical Research** will be held January 30 and 31, 1953, at Carmel, California.

* * *

The 19th annual meeting of the **American College of Chest Physicians** will be held at the Hotel New Yorker, New York City, May 28-31, 1953. Physicians who wish to present papers at the meeting should submit titles and abstracts to Dr. Arthur M. Olsen, chairman of the Committee on Scientific Program, American College of Chest Physicians, Mayo Clinic, Rochester, Minnesota.

* * *

Outstanding leaders in medicine and medical education will be featured on the program of the 1952 annual session of the House of Delegates of the **Student American Medical Association,** December 29-30, at the Sheraton Hotel, Chicago.

Dr. Walter C. Alvarez, Chicago, will speak December 30 on "The Disappearing Art of Diagnosis with the Eyes and Ears." Dr. John Van Nuys, dean, Indiana University School of Medicine, will be the principal luncheon speaker the same day, discussing "A Dean and His Problems."

* * *

The Joint Meeting of the **California Society of Pathologists** and the Southwestern Region of the College of American Pathologists will be held in San Francisco, December 6-7, 1952, in conjunction with the Semi-annual Slide Conference sponsored by the Cancer Commission of the California Medical Association.

# INFORMATION

## Income Taxes—Division of Fees

A RECENT RULING by the Bureau of Internal Revenue regarding the taxation of fees that are divided amongst two or more physicians has only partial application in California owing to the "anti-rebate law" in effect in this state.

Briefly, the Bureau of Internal Revenue has ruled that physicians may deduct from their taxable income payments they make for "professional assistance" in conducting their practices, and that likewise physicians may deduct as a business expense payments made to other physicians as compensation for referrals; *provided* that the payment of such "referral fees" does not "frustrate sharply defined national or state policies . . ." In this regard, the Bureau ruling follows the law laid down by the U. S. Supreme Court in *Thomas B. Lilly case,* where it was held that an optical company could deduct rebates paid to physicians who prescribed eye glasses and who referred their patients to the optical company. A major consideration in the U. S. Supreme Court decision permitting the deduction as a business expense of eye glasses rebates was that in the state in which the rebates occurred the rebates were not illegal.

In this connection it must be pointed out that, in California, Sections 650-654 of the Business and Professions Code expressly prohibit the payment or receipt of any unearned consideration or rebate "for referring patients . . . to any person . . ." Therefore, in California it is illegal for one physician to pay another a portion of a fee collected solely as a reward to the physician receiving the payment for having referred a patient to the physician making the payment.

Hence, the recent Bureau of Internal Revenue ruling will not apply in California insofar as "referral rebates" are concerned; such rebates or payments, being in violation of state law, will not be a deductible business expense.

On the other hand, the first part of the Bureau of Internal Revenue ruling to the effect that payments made by physicians to other physicians as compensation for work actually performed are deductible business expense, will apply in California, because our "anti-rebate law" does not apply where the payment is made for services rendered rather than for the act of referral.

## California Physicians and Civil Defense

*Prepared by Medical and Health Services, State Office of Civil Defense*

IN ATTEMPTING to present a view of the medical and public health part of civil defense plans there is, on one hand, the risk of assuming too little familiarity with the subject on the part of physicians and workers in fields allied to medicine—this assumption resulting in a seeming, although unintended, insult to their intelligence—and on the other hand there is the equally likely fault of over-assumption of knowledge with the result that the presentation will not easily be followed or understood. Apologies are therefore offered at the outset for either or both of these offenses.

The California State Civil Defense and Disaster Relief Plan is based upon the California Disaster Act of September 15, 1945, and the Civil Defense Act of October 2, 1950.

The Director of Civil Defense of California, in transmitting the plan to the Governor, pointed out that it is "advisory in character to political subdivisions below state level, in recognition of their autonomy" but that adherence by these subdivisions "to the basic organizational structure and procedures set up will provide the uniformity and standardization essential" to an effective working of the plan in the event of a disaster.

The Governor, in his foreword to the publication of the plan, stresses that it "is based upon the fundamental precepts of civil defense—self-help and mutual aid. It preserves the historic autonomy of the community, but pledges the entire resources of the State in the event of emergency beyond the capabilities of a single community or a group of communities banded together for mutual assistance. Its success depends upon thorough and intelligent planning and full cooperation at all levels of government."

The Medical and Health Services organization and effort are, of course, but a part—a vital part—of the over-all state plan which includes such other—and all of them interrelated, variously interdependent—services as: welfare and evacuation, communications, transportation, utilities, engineering, supply, fire, radiological defense, law enforcement, training and public information services.

The plan assumes:

(a) that war may involve enemy action against the civilian population and property,

(b) that sabotage is a major enemy policy and capability,

(c) that atomic weapons will be employed against the most strategic installations and densely populated areas,

(d) that evacuation of elements of population centers will occur only when there is a threat of sustained heavy enemy air attack or invasion in force.

The total plan is based on the worst combination of disaster circumstances that can reasonably be expected; almost the worst that can be imagined. We all know what can happen to "best laid plans," but if we look upon this plan as a form of insurance to protect the lives and health of the people of California, we need not regret any eventuality that will have made the plan excessive in relation to reality any more than we should regret expenditures on life insurance, car insurance, or fire insurance or fire precautions just because we didn't die or become involved in a collision or because our house was only partially burned down or didn't even have a fire. The plan is adaptable to peacetime disaster as well as to war conditions. In time of war it would contribute greatly to the war effort by saving the lives and conserving the manpower that produces the war potential.

The fundamental problem is the quick expansion of existing medical and public health resources in time of disaster to meet the task of caring for casualties in numbers multiplied many times beyond the capacity of our present resources, and to maintain or restore under the temporary disruption of normal sanitary service and the sudden displacement of possibly hundreds of thousands of persons in the state, the safeguarding of food, milk and water and the employment of other measures to prevent the spread of communicable disease.

An atomic attack will mean a quick overflow of the entire present hospital bed capacity of the state, requiring the immediate establishment of auxiliary hospitals in the vicinities of existing hospitals to provide their additional bed-needs, and of large numbers of improvised hospitals to supplement existing hospitals, in a variety of buildings, such as schools, hotels, motels, universities, and apartment buildings in locations surrounding the stricken areas.

An attack will call for the services of every workable doctor, dentist, nurse, pharmacist, technician, veterinary and mortician in the state, besides the special and limited services of those doctors and nurses who through reasons of health and age are only partially workable. Also, it will call upon many thousands of non-professionals for the work of litter bearers, aides, ambulance drivers, clerical and many other forms of help.

Estimates of casualties, including destruction of medical personnel, and of property damage including destruction of metropolitan hospitals and facilities, are based on what actually happened in the two Japanese cities from two atomic bursts. Since the time of those two bursts a great many American medical minds have been occupied with studies as to what would happen to the populations of American cities similarly attacked; what would happen with no preparation or planning and, as was the case in Japan, no knowledge of how radiation victims could be rescued and radiation fatalities greatly reduced.

Important lessons have come from the war experiences in England where civil defense medical and health organization turned the early chaotic condition into one of great efficiency and smooth order. Even with the conventional "pre-atomic" bombs and rocket bombs that were rained on England there was seen the instant need for a thorough organization of medical and health effort in England and, once it was developed, everyone saw its importance and necessity. In one night, in Coventry, in 1940, bombs killed 22,000 and injured 28,000 persons. Civilian casualties treated at first-aid posts and first-aid mobile units in all of England throughout the entire war amounted to 165,000 persons. But that number would be exceeded in one day in Los Angeles or San Francisco by the dropping of one atomic bomb. This comparison gives some indication of the difference in magnitude of the medical job and the need for civil defense organization in any future war.

This lesson has led, in every city and region of the United States, to a growing force and volume of planning and preparation, all aimed at the goal of minimizing human loss both from casualties in possible bomb areas and from the gathering toll of disease and strain that would follow upon the sudden displacement of enormous numbers of our citizens.

If a task of this magnitude is to be faced realistically, and if the plan, therefore, is to envisage the pressing into service of every unit of medical manpower in the state and the use of every conceivably available item of equipment and facility plus the stockpiling in strategic storehouses of all materials that would be of vital need, then the plan must be statewide with a certain amount of coordination at the center and with a great deal of cooperation and hard work throughout the whole medical structures of the local regions.

This effort must, and does, include such items as:

(a) A survey of all available resources (personnel, supplies, present facilities).

(b) The allocation of available resources under a plan that sees attacked areas helped by the neighboring unattacked areas.

(c) Alternate medical teams to fill the gaps caused by death, injuries and displacement of individuals of present teams.

(d) Agreements for mutual aid.

(e) Selection of auxiliary facility sites.

(f) A "spot map" of existing and auxiliary facilities.

(g) Measures for detection and prevention of spread of communicable diseases.

(h) An adaptation of food, milk, and sanitation practices to fit disaster needs.

(i) Nutrition problems in emergency rations.

(j) Mental hygiene measures in the control of panic and to meet psychological warfare.

(k) Establishment of a record and reporting system.

(l) Maintenance of vital records in the listing, identification and disposition of the dead, with notification of the next of kin.

(m) Training and public information.

(n) Radiological defense, which is so highly specialized as to require a special organization, closely allied to, closely cooperating with the medical and health service, but necessarily separated from it in organization.

Coordination from regional and state levels, both in planning and operation, is, by the very nature of the effort, an inescapable part of a medical and health program for civil defense. To some few members of the medical and allied professions, as well as to some in all other walks of American life, the word "coordinator" has come to have an unsavory connotation, perhaps not wholly undeservedly; it has become a frightening word and, to some few, a fighting word. In speaking of civil defense planning to date, there has been some reference to the "confusion at the top and apathy at the bottom." Both confusion and apathy are regrettable in any part of the structure; neither can be denied; both of them, to the extent that they exist, are such natural human imperfections as to call for no explanation or discussion.

As we emerge from the blueprint stage—and we have well emerged from it—the element of confusion is in a satisfying state of decline and apathy is being replaced by an awakening interest.

As we pass from the talking and paper stage of placing orders for supplies and equipment to the stage of filling storehouses with them—a condition now being realized—and as we pass from nebulous hypothetical medical team organizations and facilities into actual specific set-ups—another condition now in realization—we have reason to hope that we are indeed approaching closer to a goal of medical preparedness. Except for the supplies and the training, everyone's deepest hope is that the whole thing can remain forever on paper.

What can those of the medical and allied professions do about it right now? They can put themselves on more familiar terms with the plan by certain readings. They can join up with units and attend meetings of groups that fit the closest to their individual capabilities and circumstances.

They can be well guided in this by their county medical societies, each of which has a committee for civil defense. Each county medical society has contact with the California Medical Association's Emergency Medical Service Committee, whose duty and desire are to assist and encourage the local county medical groups in civil defense planning. This committee is represented on the Medical Advisory Committee of the Disaster Council for the State of California and cooperates with city and county and state health departments.

Among the items of suggested reading are the two articles by Dr. Justin J. Stein in CALIFORNIA MEDICINE of November 1950 and January 1952, respectively, and the editorial "Civil Defense — An Urgent Medical Problem" in the same journal, December 1950.

Also for recommended reading, study, and reference, there should be listed:

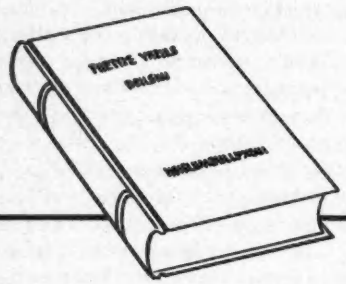
(a) Medical Aspects of Atomic Weapons—Bulletin of the Los Angeles County Medical Association, September 7, 1950.

(b) Civil Defense Against Atomic Attack—U. S. Government Printing Office.

(c) Manual for Organization, Training and Operation of First-Aid Stations, recently issued by the Division of Medical and Health Services of the California State Office of Civil Defense.

(d) Plan for Existing, Auxiliary, and Improvised Hospitals—now on press and shortly to be issued by the California State Office of Civil Defense.

(e) Plan for the Blood Program under Disaster Conditions — Federal Civil Defense Administration —U. S. Government Printing Office.



# THE PHYSICIAN'S *Bookshelf*

**COWDRY'S PROBLEMS OF AGING—Biological and Medical Aspects—Third Edition.** Edited by Albert I. Lansing, Ph.D., Washington University, St. Louis, the Williams and Wilkins Company, Baltimore, 1952. 1,061 pages, $15.00.

The third edition of the most authoritative treatise on the biology of aging brings to this important subject new and cogent information for the gerontologist. This is an essential volume for all physicians, not even excluding the pediatrician, because of its basic descriptions and data concerning fundamental problems of growth, development, and senescence. Here is assembled information concerning the comparative physiology and biochemistry of the mammalia, which is pertinent to the most important problems dealing with the finiteness of these species. Man is destined to age at rates characteristic for his type and conditioned by his hereditary legacy. The factors which influence the progress of this inevitable deterioration in an infinite universe are discussed with the wisdom, detachment and objectivity characteristic of philosophers who deal abstractly with a thesis. This book offers for the physician what the concept of rejuvenation might offer for those who feel that rejuvenation would supply them with a vigor beyond that which they might achieve as the natural consequence of experience and aging. The third edition differs considerably from the preceding editions; it does not supplant them, it embellishes them. It adds to the basic discussions those arguments and data which demonstrate that the concept of the aging process is not only one of constant evolution, but one in which active research is both simplifying and complicating the problem with the assurance ultimately of greater comprehension. A very valuable book which must be read to be appreciated, and an important addition to the library of a physician.

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**SYNOPSIS OF GENITO-URINARY DISEASES—Fifth Edition.** Austin I. Dodson, M.D., F.A.C.S., Professor of Genito-urinary Surgery, Medical College of Virginia; and Donald L. Gilbert, M.D., Instructor in Urology, Medical College of Virginia. The C. V. Mosby Company, St. Louis, 1952. 313 pages, $4.00.

The Fifth Edition of Dodson and Gilbert, "Synopsis of Genito-urinary Diseases," is an excellent, concise and inexpensive book on urologic diseases. This volume, only slightly changed from the previous editions, has been prepared for the medical student or as a handy reference for the general practitioner. It is a small, easily handled book, having a good index, and covering a surprising number of subjects in a brief but adequate manner. There are chapters on urologic diagnoses, cystoscopic instruments, the need for cystoscopy, anatomy of the genito-urinary tract, and a discussion of most of the common diseases seen by the urologist.

This is a valuable book and will make a desirable addition to the library of the man practicing general medicine or surgery.

**THE TOXEMIAS OF PREGNANCY—Second Edition.** William J. Dieckmann, S.B., M.D., Mary Campau Ryerson Professor and Chairman of the Department of Obstetrics and Gynecology, University of Chicago. The C. V. Mosby Company, St. Louis, 1952. 710 pages, 85 illustrations, $14.50.

This is an extended version of the first edition, which appeared in 1941, and includes in the 200 added pages at least brief reference to practically everything which has been written regarding toxemias in the last decade. To readers of the previous edition it may be said that the revision is a similar encyclopedic recitation of facts and figures, put together without much transitional phraseology or topical organization, all of which makes for tiresome and difficult reading. However, practically everything pertaining to the subject has been set down, and no doubt those who are actively delving into the mysteries of the toxemias will be delighted to find so much compressed into 700 pages.

As in the first edition, the various chapters are grouped into six sections, the first of which deals with four somewhat unrelated phases of the situation, namely, history, classification, geographical distribution, and pathology. This is followed by a lengthy exposition concerning the almost endless array of physicochemical determinations which have been so popular with investigators in this field but which have yielded so little of lasting value to the clinician. Additional pathologic items, as well as an endocrine chapter, are thrown in with the physiologic material. Section III is concerned with the etiology of eclampsia, but regrettably the reader is not rewarded by finding here any concise presentation of the author's current views on the sequence of events leading to the classical clinical picture of eclampsia.

The next two sections are devoted to the clinical aspects of toxemia and to its treatment. The material on therapy is unnecessarily confusing and repetitious, owing to the separate considerations of convulsive and non-convulsive toxemia. The final section deals with maternal and fetal mortality and also with prenatal care—a subject which might be disposed of briefly earlier in the book. The last two pages of the text will be passed over quickly by the research worker, but should prove to be of particular interest to physicians in California where malpractice insurance rates are soaring to astronomical heights. These pages describe certain legal pitfalls which have trapped unwary obstetricians, although some of the examples quoted seem to have little or nothing to do with the subject of toxemia.

This monograph for the most part is quite uncritical and lacks adequate summarizations of what the author considers important in the tremendous mass of material which he has sifted. As a reference work for the investigator or teacher it now enjoys, of course, a monopoly in its field, particularly because there has been no second edition of the less ambitious but more readable volume by Dexter and Weiss (1941). For other purposes it cannot be seriously recommended.

**WHEN DOCTORS ARE PATIENTS.** Edited by Max Pinner, M.D., and Benjamin F. Miller, M.D. W. W. Norton & Company, Inc., New York, 1952. 364 pages, $3.95.

A doctor is first of all a person, and, it follows, a group of doctors represents a cross section of humanity. The truth of this generality is a by-product of—and perhaps the most interesting thing about—the book, "When Doctors Are Patients."

To illustrate this truth was not the purpose of the book. The senior author presents it in "the hope that the method of inquiry will be useful in defining . . . the subjective experience of disease, and, therewith, a broader field for therapeutic activities." From the scientific viewpoint it asks two main questions: (1) How does an individual's personality modify his disease? and (2) how does the disease modify the individual's personality? The thirty-three autobiographical sketches of disease by physicians who, themselves, have suffered give some provocative data.

To the reviewer, however, the scientific values seem comparatively insignificant compared to the human interest. The art, rather than the science of medicine predominates. Too much variation of topics, individuals, and conditions is involved to make a statistical imprint. The variation itself is impressive: one man writes a straightforward account of his experience with a serious and lethal or disabling disease, commenting on it with amazing objectivity; another writes round and round about his comparatively minor disease, rarely getting to the basic condition but allowing his imagination full sway.

The book, with its wide appeal, may be enjoyed by the layman as well as the doctor. The majority of the stories are well written. All who read it can learn from it: sick doctors—like all sick people—are often remarkably egocentric; and, like other patients, want and appreciate a kindly interest in and something done for their symptoms. The physician may well find here the reflection of his own ailments. The experience of his colleagues seems to say, "There but for the grace of God go I." And in this humility he may benefit.

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**THE PREVENTION OF RHEUMATIC FEVER**—Lowell A. Rantz, M.D., Associate Professor of Medicine, Stanford University School of Medicine. Charles C. Thomas, publisher, 1952. 66 pages, $2.25.

In this volume of 59 pages Rantz gives definite information as to the etiology, epidemiology and prevention of rheumatic fever as related to the Group A hemolytic streptococci.

Clinical recognition of an invasion by the Group A hemolytic streptococci is made by three signs: (1) exudative tonsillitis, (2) marked redness and edema of the pharyngeal soft tissues, particularly the soft palate and pillars, and (3) tender anterior cervical adenitis. A direct swab taken from the pharynx by the oral approach and streaked directly on blood agar plates will give laboratory confirmation of the clinical diagnosis.

The goal of the physician is to prevent infection by hemolytic streptococci by isolation from the acutely ill and suspected carriers. If active hemolytic streptococci invasion occurs, then the prevention of rheumatic fever can be accomplished in practically every case by the multiple injection of the procaine salt of penicillin suspended in oil and aluminum monostearate so that an antistreptococcal concentration is maintained for five to seven days. This can be accomplished by 600,000 units given intramuscularly every other day for two or three doses; 200,000 units orally five times daily (1,000,000 units per day) for seven days is effective.

The monograph is clearly written and is filled with practical suggestions for the general practitioner to whom falls the duty of the prevention of rheumatic fever.

**MEDICAL BIOGRAPHIES—The Ailments of Thirty-three Famous Persons.** Philip Marshall Dale, M.D., University of Oklahoma Press, Norman, Okla., 1952. 259 pages, $4.00.

In this volume Dr. Dale reveals a talent for the art of the short story which offers a real challenge to the most seasoned professional writer. Fascinatingly told are the vital and final episodes in the lives of 33 famous persons, many of whom were responsible for and some of whom altered the course of history and civilization. Many are included whose accomplishments in politics, literature, poetry, philosophy, military tactics, art and science were outstanding. Here is recorded and retold in pertinent clinical histories the last hours and fate of those finite lives which were entrusted with the destiny of man. Inadvertently, these histories reveal the arduous path through which the principles of clinical medicine and differential diagnosis were developed. A review of these anecdotes indicates the marvelous advances which have been made and the legacy of modern medicine. What science and research have made available to the modern physician is magnified by the appreciation of those infirmities of the great of the past who groped hopelessly and often aimlessly before the simplicity of nature's pattern in the absence of definitive diagnostic method. A fascinating book, which is highly recommended to the apprentice, the journeyman and past master, for information, inspiration, and sheer delight.

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**REACTION TO INJURY—Pathology for Students of Disease—Volume II—The Reactions of Submission and Adaptation and the Disease Entities Arising Out of Their Elaboration**—Wiley D. Forbus, M.D., Professor of Pathology, Duke University. The Williams and Wilkins Company, Baltimore, 1952. 1110 pages, 836 illustrations, 54 in color, $20.00.

This book represents a new and interesting approach to pathology and its clinical applications. Rather than being a rigid and formal presentation of gross and microscopic pathology, with emphasis on cellular details, it is a dynamic approach to the use of pathology in correlating function with organ alterations in disease. Disease is interpreted from the initial viewpoint of relevant facts in biochemistry, anatomy, and physiology, etiological factors are discussed, and the consequences in terms of function and altered tissue structure are elaborated. It is, therefore, a type of book which can serve as a text in pathology, fundamental clinical medicine, or pathological physiology.

The material covered in this volume deals with disturbances in metabolism, vitamin deficiencies, blood dyscrasias, endocrine imbalances, congenital dysplasias, and disturbances in growth and development. Functional and structural adaptation to diseases in the circulatory system, lungs, and viscera are discussed. The central nervous system is very briefly covered.

The book is bulky and expensive, but considering its value both as a pathology text, an interpretive correlation of clinical medicine and pathological physiology, and its delightfully stimulating approach to disease it is fully worth the cost.

Medicine is constantly changing. The student will find this volume an excellent place to embark upon the study of disease; the practicing physician will find many delightful hours in reliving much of his former medical experience in the light of changing concepts of disease causation by the study of this volume, and his practice and approach to clinical problems will thereby be enriched. The reviewer recommends the book, is happy to keep it on his shelf for reference work, and enjoys browsing through it when leisure time invites creative reflections about pathology and medicine.

**A TEXTBOOK OF PATHOLOGY—7th Edition.** E. T. Bell, M.D., Emeritus Professor of Pathology, University of Minnesota. Lea and Febiger, Philadelphia, 1952. 1008 pages, 529 illustrations, 5 color plates, $12.00.

This is one of the standard American textbooks of pathology which is basically unchanged in the new edition. Twenty-seven of its thirty chapters are again written by Bell, the rest by his colleagues Clawson and McCartney. Downey is accredited with revision of the chapter on *Blood*. It presents a reasonably full account of elementary facts of human pathology. The text has been expanded by about 100 pages. The illustrations continue to be numerous and admirably reproduced. References to the literature are conveniently located after many of the subdivisions of chapters and classical writings are listed frequently if not regularly. The organization of the text is conventional, approximately half the material being presented according to organ systems. There is a well-advised section on the *Value of the Biopsy and How It Should Be Performed* but this is appended to the end of the chapter on *Tumors* and the broader aspects of the value and use of the biopsy in diagnosis are neglected. The structure and content of the book make it a useful handbook to the beginning student. As an introduction to the study of disease on a scholarly plane, it has certain shortcomings. There is a conspicuous lack of anything to orient and shape the attitudes of students entering upon a new and unfamiliar field. The reader is thrust immediately into definitions of special terms in the all-too-brief introduction without benefit of any reflections on the nature and significance of disease. This is exemplary of the categorical character of the text as a whole. The disposition of the subject matter appears ill-chosen in some instances. For example, the discussion of Hemorrhagic Diseases is a subdivision of the chapter on *Circulatory Disturbances*. Disturbances in the metabolism of electrolytes and the pneumoconioses are discussed in a chapter entitled *Retrogressive Tissue Changes*, which are by and large those structural changes in the cell that are the hallmark of injury from a wide variety of causes. *Diseases Due to Deficiency of Vitamins* are described but no other forms of nutritional deficiency in any one section. Hypersensitivity is relegated to a brief paragraph in a section of *Immunology* without being given due consideration as a mechanism of disease. About twenty pages are given to descriptions of some of the viral and rickettsial infections in the chapter on *Bacterial Diseases* but only one page is devoted to a discussion of the broad aspects of the problem of viruses. General remarks on tumors are more adequately presented, comprising about eighteen of the 150 pages on *Tumors*. There is nothing in the style to make this book appreciated as medical literature.

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**FORENSIC MEDICINE—2nd Edition**—Keith Simpson, M.D. (Lond.), Reader in Forensic Medicine to the University of London. Edward Arnold & Co., London (Williams and Wilkins, Baltimore), 1952. 344 pages, $4.50.

This second edition of an excellent textbook provides a brief and essentially practical guide to current teaching in forensic medicine.

While the legal premises are fundamentally those of England and Scotland, the work should serve as a reliable guide to the physician in his contacts with the law arising out of his practice.

Several sections, notably those dealing with death under anesthesia, asphyxia, and industrial injuries, have been rewritten and statistics have been brought up to date. Discussion of laboratory procedure (which in practice properly belongs to the specialist) has been kept to a minimum.

The subject matter is presented in a vivid and interesting manner.

**SHOCK TREATMENTS, PSYCHOSURGERY AND OTHER SOMATIC TREATMENTS IN PSYCHIATRY—2nd Revised and Enlarged Edition**—Lothar B. Kalinowsky, M.D., Research Associate in Psychiatry, Colllege of Physicians and Surgeons, Columbia University, and New York State Psychiatric Institute and Hospital; and Paul H. Hock, M.D., Principal Research Scientist (Psychiatry), New York State Psychiatric Institute and Hospital; Assistant Professor, College of Physicians and Surgeons, Columbia University. Grune & Stratton, New York, 1952. 396 pages, $8.75.

The second edition of this volume has been revised and enlarged, particularly in the description of psychosurgery. There is no doubt that this is the most thorough and comprehensive book available on the general theme of physiological treatment in psychiatry. Beginning with an account of the historical development of these therapies, the authors proceed to outline in detail the literature on the subject of insulin and convulsive therapies, indicating the various techniques and modifications, complications, therapeutic results, psychological, neurological and laboratory observations, and add their own opinions of and critical comments on these procedures. The chapter on psychosurgery is admirably written, and techniques such as a standard procedure, partial lobotomy, leukotomy, gyrectomy, topectomy, cortical undercutting, thalamotomy, and transorbital lobotomy; complications, physical, neurological and psychological changes resulting, and therapeutic results in schizophrenia, affective disorders and psychoneuroses, are all presented.

Somatic methods of treatment in psychiatry are not new, but the present-day application of the so-called "drastic therapies" is about sixteen years old. There are other somatic therapies other than the shock therapies, and psychosurgery and the use of narcotherapy, drugs like benzedrine, acetylcholine, histamine, myanesin and glutamic acid, besides such treatment as nitrogen inhalation therapy, carbon dioxide and ether are outlined. The "Antabuse" therapy of alcoholism developed in recent years is also given. The many theories offered to explain the modus operandi of these treatments are discussed, and the authors conclude by stating "at present we can say only that we are treating empirically disorders whose etiology is unknown, with methods such as shock treatments whose action is also shrouded in mystery." The bibliography is detailed and excellently chosen. This volume remains the most comprehensive and authoritative in the field.

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**TEXTBOOK OF MEDICINE—10th Edition**—Edited by Sir John Conybeare, K.B.E., M.C., D.M.(Oxon.), F.R.C.P., Physician to Guy's Hospital, London; and W. N. Mann, M.D.(Lond.), F.R.C.P., Assistant Physician to Guy's Hospital. The Williams and Wilkins Company, Baltimore, 1952. 912 pages, $8.00.

The tenth edition of this textbook of medicine appears three years after the publication of the ninth edition. There is, for the first time, a coeditor in Dr. W. N. Mann, a colleague at Guy's Hospital.

The new edition embodies revision and some rewriting in many sections. It is interesting to find that many of the items singled out for criticism in review of the ninth edition in California Medicine (71:317, Oct. 1949) have been corrected: For instance, a new appendix has been added on the sulfonamides and antibiotics (attempting to summarize the position at the date of going to press); there has been improvement of the sketchy section on endocrinology; propylthiouracil is now advocated instead of thiouracil in the therapy of thyrotoxicosis; and croton oil purgation is no longer recommended for cerebral hemorrhage.

As noted in our 1949 review, this book is primarily a text for the British medical student. It will still bear reading by the American physician for comparison and interest.

**STEREOENCEPHALOTOMY (Thalamotomy and Related Procedures) Part I—Methods and Stereotaxic Atlas of the Human Brain.** E. A. Spiegel, M.D., Professor of Experimental and Applied Neurology, Head of the Department of Experimental Neurology, Temple University School of Medicine and H. T. Wycis, M.D., F.A.C.S., Clinical Professor of Neurosurgery. Grune & Stratton, New York, 1952. 176 pages, $8.00.

This volume summarizes an extensive program of research in a new and rapidly developing field of neurosurgery. The methods and equipment developed serve as the basis for future clinical investigation. There is little doubt concerning the value and great therapeutic possibilities of this method.

The authors have produced a stereotaxic atlas of fundamental importance to those interested in this phase of neurosurgery. This volume is part one of a series. Subsequent parts yet to be published will deal with clinical problems and should prove of greater general interest to the profession.

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**DISEASES OF THE NERVOUS SYSTEM — Described for Practitioners and Students—7th Edition.** F. M. R. Walshe, M.D., D.Sc., F.R.C.S., Fellow of the Royal College of Physicians of London. The Williams and Wilkins Company, Baltimore, 1952. 365 pages, $5.50.

This work is intended to be "a simple textbook adapted to the needs of the student and practitioner," and in this it meets its purpose. It is not all inclusive but deals with those diseases most commonly met in practice and with the methods of treatment and diagnosis which are most useful in the general practitioner's hands. It is lucidly written, avoids complex terminology, and contains no bibliography. Neurologic disorders are presented as fluid states and not as "anatomical moulds."

Of particular value are those sections which differentiate organic from functional features in the history and examination. The author is to be commended upon the repeated stress placed upon the avoidance of producing psychological invalidism by ominous prognoses and restrictions, and of sparing the patient valueless but "traditional" treatments when his resources could be better utilized in other ways.

There are a few qustionable points such as failure to consider the place of surgery in the treatment of cerebral aneurysm and the inclusion of psychomotor epilepsy under "post-epileptic automatism," but these detract little from the value of the book.

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**PROGRESS IN NEUROLOGY AND PSYCHIATRY—An Annual Review—Volume VII**—Edited by E. A. Spiegel, M.D., Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine. Grune & Stratton, New York, 1952. 604 pages, $10.00.

The bulk of this volume is a tribute to the amount of work which is being done each year in the field of neurology and psychiatry. As must always be the case, the various chapters reflect the personality and ability of the particular author responsible for their compilation, and thus vary greatly in quality. However, the general level is high, and for this reason the reader who would like an encyclopedic view of the whole field and has the staying power to plow through the volume should gain his objective. However, it will be a rare physician who will possess this stamina, and for this reason it is probable that the book is of more value as a reference work. In this regard, the necessary limitations of space are a handicap, so that it must serve the purpose largely of an annotated bibliography, saving the reader the necessity of perusing the more ponderous indexes. It seems to this reviewer that the endeavor to produce a volume that gives the whole picture in a readable form, yet is detailed enough for the specialist, is doomed from the start. The present work has made a valiant attempt at this hopeless task.

**LIVING WITH DIABETES** — Edward Tolstoi, M.D., Crown Publishers, Inc., 419 Fourth Ave., New York 16, 1952. 90 pages, $2.00.

In this easily readable short (87 pages) book, Doctor Tolstoi presents his views of diabetic treatment to the lay reader. Actually Doctor Tolstoi probably used more words than were necessary since the entire substance of his book is this—take insulin regularly, eat about what you want, and don't worry about spilling sugar.

Whether Doctor Tolstoi is right or not in his assumption only time will tell. However, it is fair to point out that at present he only claims fifteen years' experience in this type of treatment, certainly too short a time to evaluate the eventual evidence of retinitis, arteriosclerosis, etc. Also, it is very disappointing to this reviewer to see the problem of the obese diabetic disposed of in one sentence.

It is obviously impossible in a review to go into the controversial aspects of diabetic treatment. One wishes however that Doctor Tolstoi would present more definite proof of his views before attempting to persuade the public that present-day methods of treatment are entirely unnecessary.

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**INTRODUCTION TO CLINICAL NEUROLOGY — 2nd Edition**—Gordon Holmes, M.D., F.R.S. The Williams and Wilkins Company, Baltimore, 1952. 189 pages, $4.00.

It is open to question whether anyone owning a copy of the first edition of this work would profit greatly from purchasing the second, since the changes made have been relatively unimportant. The book is a small one, written in simple language which should be readily understood by the medical student embarking on his study of neurology. Yet it contains the experience of a great master in the field, and can be read with profit by the specialist as well. The objective of the book is to teach the elicitation and interpretation of neurological signs, rather than to describe neurological diseases and their treatment. Thus it in no way presumes to take the place of a neurological text. It is preeminent in its field, and can be highly recommended to the medical student, the practitioner who would like to sharpen up his neurological acumen, and most of all the neurologist who at some time had the privilege of making ward rounds with the author.

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**DIAGNOSTIC ELECTROENCEPHALOGRAPHY**—Hans Strauss, M.D., Associate in Neurology, Mount Sinai Hospital; Mortimer Ostow, M.D., Med.Sc.D., Adjunct in Neurology, Beth Israel Hospital and Mount Sinai Hospital; and Louis Greenstein, M.D., Adjunct in Neurology, Mount Sinai Hospital, New York City. Grune and Stratton, New York, 1952. 282 pages, $7.75.

The field for books dealing with electroencephalography has, in the opinion of this reviewer, been pretty well worked out, and might be allowed to remain fallow for a while. The volume under discussion presents nothing that is not already available in standard works on the subject. Certain of the instructions regarding technic would not be agreed to by many workers of experience in the field, yet are set down in a rather dogmatic fashion. This dogmatism is carried into details with which the authors seem obviously unfamiliar. Thus, in speaking of the use of needle electrodes, which are not favored save in "unconscious or restless patients," they recommend the use of eighteen gauge hypodermic needles. Such large needles, suitable for a transfusion, are obviously not to be used as electrodes, so that one wonders how much experience the authors have actually had with needle electrodes.

In spite of such minor discrepancies, the book is an adequate text in the field, and contains good illustrations and an admirable bibliography.

**BIOCHEMISTRY AND HUMAN METABOLISM.** Burnham S. Walker, M.D., Ph.D., Professor of Biochemistry; William C. Boyd, Ph.D., Professor of Immunochemistry; Isaac Asimov, Ph.D., Assistant Professor of Biochemistry, all at Boston University School of Medicine. The Williams and Wilkins Company, Baltimore, 1952. 812 pages, $9.00.

The foreword by John T. Edsall expresses well the purpose and spirit of this book. He describes the book as having a freshness and vitality in its outlook and presentation which is distinctive among biochemistry textbooks written for medical students. Professor Edsall further expresses his enthusiasm in that the first chapter is devoted to proteins, the basic material in cell structure and function. The authors do not attempt to precisely define proteins, but describe them as "large molecules, of molecular weight of the order of several thousand to several million, occurring in the tissues of plants and animals and containing carbon, hydrogen, oxygen and nitrogen, and sometimes other elements, and constructed largely from amino acids." This definition differentiates proteins from other compounds of biological interest, although not by any means describing this class of substance, whose members differ so much from each other.

There are three major attributes of biological chemistry discussed: structure, function and pathology. Structure is explained in the four chapters of Part I which describe proteins and amino acids, protein structure, tissue chemistry, and blood and the anemias. The discussion of function requires fourteen chapters, grouped into Part II, Control; Part III, Growth; and Part IV, Metabolism. Two chapters of approximately fifty pages each are devoted respectively to enzymes and to hormones, which control the rate and direction of the chemical reactions occurring in metabolic processes. These two chapters describe the basic chemical processes catalyzed by enzymes and hormones, as well as the structure and nature of the catalysts themselves. It is furthermore made clear that although there is an apparent static structure of the human body, it is in reality "a system in which the various components are in a state of flux and are related to and depend upon one another in complex fashion. Nothing in the body remains static, not even the inorganic constituents of the bones and teeth." The book deals with the body as a "dynamic phenomenon."

Part V, Pathology, contains the excellent Chapter 19 on Vitamins and Vitamin Deficiency Diseases, and Chapter 20, which discusses the physiology and theoretical chemistry of infection in a disappointingly general and sketchy manner.

Part VI is an appendix of four chapters on the physical chemistry of protoplasm. The authors are to be congratulated on their pedagogical insight and courage indicated by their placing this discussion at the end of the book. In so many books and university courses in biochemistry the reader or student is bored and frightened by the complex physical chemistry formulas and equations, so that he thumbs through the rest of the book listlessly or he takes lecture notes in a state of harassment because of his confusion. The authors of "Biochemistry and Human Metabolism" catch and hold the reader's interest because each step in the development of the subject is simple and clear, with few exceptions.

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**PHYSICAL MEDICINE IN GENERAL PRACTICE—3rd Edition**—Edited by William Bierman, M.D., and Sidney Licht, M.D., Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, 1952. 798 pages, $12.50.

This third edition is an entirely new book both in content and authorship. It has separate chapters by 22 authorities covering almost every aspect of rehabilitation. The book is divided into two sections—"methods" and "clinical applications." Under "methods" the routine aspects of physical therapy are adequately covered such as heat and cold, hydrotherapy, diathermy, ultra-violet radiation, and massage. Moreover, there are excellent chapters on the new and less-known methods such as ultra-sound, manipulation, functional muscle testing, exercise, and medical rehabilitation. The chapter on manipulation is one of the few good expositions of this controversial subject and should be read and studied by every physician dealing with musculo-skeletal disorders.

The wide spectrum of conditions covered under "clinical applications" ranging from eye to genito-urinary diseases gives proof to the statement that physical medicine has outgrown the concept of adjunctive therapy in orthopedics to become the broadest of the clinical specialties. Also physical medicine should and does consist of more than heat and massage and thus requires medical planning and supervision.

All in all, this book is one of the best now available in its field and is to be highly recommended to general practitioners and also specialists in neuromuscular and musculoskeletal conditions.

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**VASCULAR DISEASES IN CLINICAL PRACTICE—2nd Edition**—Irving Sherwood Wright, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College. The Year Book Publishers, Inc., 1952. 552 pages, $8.50.

The second edition of this fine book has lost none of the compactness which characterized the first edition and which made it a concise source of information for those involved in the practice of clinical medicine. Chapter II embracing the history and physical examination as well as special study of the patient with vascular disease is eminently worthwhile reading for any physician in clinical practice regardless of specialty. The chapters allocated to arteriosclerosis and thromboangiitis obliterans are excellent and the selections on safeguards and therapy are extremely wise especially in regard to the use of vasodilators and sympatholytic drugs. Material has been added describing the more recent developments in the field of lipid metabolism in relation to arteriosclerosis. Other new material concerns the relation of ACTH and cortisone to the therapy of thromboangiitis obliterans, scleroderma, essential polyangiitis, and disseminated lupus. The anticoagulants Tromexin, Paritol, Hydroxycoumarin are also discussed at some length. Sections on amputation and cryoglobulinemia are also new to this edition. In general it can be said that Dr. Wright has made a successful effort to cull the most important and the most essential material available to provide a text of unusual aid for the practitioner of medicine.

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**THE PATHOLOGY OF DIABETES MELLITUS—3rd Edition**—Shields Warren, M.D., Sc.D., Departments of Pathology of the New England Deaconess Hospital and the Harvard Medical School; Director of the Division of Biology and Medicine, U.S. Atomic Energy Commission; and Philip M. LeCompte, M.D., Departments of Pathology, Falkner Hospital and Harvard Medical School, Boston. 112 illustrations and 3 colored plates. Lea & Febiger, Philadelphia, 1952. 336 pages, $7.50.

Doctor Warren and Doctor LeCompte have done a beautiful job of describing the various pathological changes found in diabetes mellitus. The subject is covered thoroughly including a description of the changes found in each organ of the body.

The only drawback of the book is that the known pathology of diabetes isn't too interesting in itself. After reading 315 pages of fairly drab pathology the only really exciting portion of the book is the three-page section on "A Unifying Concept of the Pathology of Diabetes Mellitus" (Chapter 28).

In summary then, this is a fine reference book but it is not recommended for entertaining reading.